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Chemical stimuli of respiration in the early neonatal period

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THREE chemical factors, hydrogen ion concentration, carbon dioxide tension (pCO_2), and oxygen tension (pO_2), adjust alveolar ventilation to the metabolic needs of the body through their action on the respiratory centers. In adults, pCO_2 of the respiratory center is believed to be responsible for the regulation of respiration under ordinary circumstances. Changes in hydrogen ion concentration may excite or depress the respiratory center indirectly by changing the plasma pCO_2, which in turn will regulate respiratory activity, or by a direct effect on the chemoreceptor reflexes in the aortic and carotid bodies. Decreased plasma pO_2 controls respiratory activity only through the chemoreceptor reflexes. For a comprehensive review of this subject the reader is referred to the section on respiration by Schmidt in Bard's Medical Physiology.[1]

The chemical control of respiratory activity is less well defined in newborn infants than it is in adults. It is the purpose

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Table I. Analgesia and anesthesia record of all mothers and birth weight of the infants

Name	*Birth weight (kg.)*	*Time of administration prior to delivery (hours)*	*Analgesia*	*Anesthesia*
1 Bri.	3.1			Nitrous oxide oxygen, Tirlene
2 Cu.	3.1	− 3	Demerol	Pudendal block; N_2O, O_2, Trilene
3 Do.	4.0	− 4¼	Demerol	Pudendal block
4 Gre.	3.1			Pudendal block; N_2O, O_2, Trilene
5 He.	3.0			Pudendal block; N_2O, O_2, Trilene
6 Ma.	3.0			Pudendal block; N_2O, O_2, Trilene
7 Sh.	2.9	− 2½	Demerol; scopolamine	Saddle block
8 St.	3.7	− 3	Demerol	Pudendal block; N_2O, O_2, Trilene
9 Su.	3.0	− 2	Demerol; scopolamine	Pudendal block; N_2O, O_2, Trilene
10 Ta.	2.5			N_2O, O_2, Trilene
11 Va. A.	2.7	− 4	Demerol; scopolamine	Pudendal block; N_2O, O_2, Trilene
12 Ak.	3.4	− 3	Demerol; scopolamine	Saddle block
13 Be.	3.1			Pudendal block; N_2O, O_2, Trilene
14 Br.	3.8	− 1½	Demerol; scopolamine	N_2O, O_2, Trilene
15 Ed.	2.3			N_2O, O_2, Trilene
16 Ka.	3.5	− 2	Demerol; scopolamine	Pudendal block; N_2O, O_2, Trilene
17 Ki.	3.0			Saddle block
18 Li.	3.0			Pudendal block
19 McG.	3.7			Pudendal block
20 Men.	3.6	− 4	Demerol	Saddle block
21 Mi.	3.7	−40/60	Na Amytal	Pudendal block; N_2O, O_2, Trilene
22 Wh.	2.6	−11	Na Amytal	Pudendal block
23 Whi.	3.2	− 1	Demerol; scopolamine	Pudendal block
24 Wi.	3.7			N_2O, O_2, Trilene
25 Wo.	3.0	− 2	Atropine	Pudendal block; N_2O, O_2, Trilene
26 Cr.	2.8			Spinal
27 Gr.	3.0	− 4	Demerol; scopolamine	Spinal
28 Bro.	3.8	−15/60	Demerol; scopolamine	N_2O, O_2, Trilene
29 Co.	2.9			N_2O, O_2, Trilene
30 Fu.	3.4			N_2O, O_2, Trilene
31 Ga.	3.9			
32 Gra.	2.7			N_2O, O_2, Trilene
33 Si.	3.0			
34 Wy.	4.4	− 6	Demerol	Pudendal block
35 Fo.	2.5			Caudal
36 Me.	3.5			N_2O, O_2, Trilene
37 Wi.	3.3			N_2O, O_2, Trilene
38 Wo.	2.5		Demerol; scopolamine	Pudendal block; N_2O, O_2, Trilene
39 Ro.	3.6			Pudendal block; N_2O, O_2, Trilene
40 Wr.	3.7		Demerol	Pudendal block; N_2O, O_2, Trilene
41 Pl.	3.3			Pudendal block; N_2O, O_2, Trilene
42 Qu.	3.4	− 2½	Demerol; scopolamine	N_2O, O_2, Trilene
43 Rob.	3.2	−11	Demerol; scopolamine	Saddle block
44 Sp.	3.3	− 2	Demerol; scopolamine	Pudendal block; N_2O, O_2, Trilene
45 Ca.	2.8	− 2	Demerol; scopolamine	Saddle block
46 Di.	3.5			N_2O, O_2, Trilene
47 He.	4.6	− 3	Demerol; scopolamine	Pudendal block; N_2O, O_2, Trilene
48 Je.	2.8			Pudendal block; N_2O, O_2, Trilene
49 Col.	3.0	− 3	Demerol; scopolamine	N_2O, O_2, Trilene
50 Pai.	3.2			N_2O, O_2, Trilene
51 Wil.	2.6			
52 Es.	2.8	− 4		N_2O, O_2, Trilene
53 Mo.	3.2	− 5½		N_2O, O_2, Trilene
54 Med.	3.0	−16¼	Demerol; scopolamine	
55 Vau.	3.0	−20¼	Demerol; scopolamine	Saddle block
56 Mar.	3.1	− 3½		Saddle block
57 Pa.	3.1	− 4½	Demerol; scopolamine	N_2O, O_2, Trilene
58 Mat.	3.9	− 3¼		Pudendal block
59 Al.	2.8	− 7		

Table I—Cont'd

Name	Birth weight (kg.)	Time of administration prior to delivery (hours)	Analgesia	Anesthesia
60 Ge.	2.9	−12		Saddle block
61 Po.	3.1	− 3½	Demerol; scopolamine	
62 Ta.	2.8	−12¾	Demerol	Saddle block
63 Co.	3.0	−18¾		Pudendal block; N_2O, O_2, Trilene
64 Car.	3.9		Demerol; scopolamine	N_2O, O_2, Trilene
65 Br. J.	2.9	− 5½	Demerol; scopolamine	Saddle block
66 La.	3.4	− 4¼		Pudendal block; N_2O, O_2, Trilene
67 Law.	3.4	− 6¼		Saddle block
68 Gr.	3.3	− 5¾		
69 De.	3.2	− 4		
70 Sm.	2.9	− 3½		N_2O, O_2, Trilene
71 Col.	3.6	− 6½		N_2O, O_2, Trilene
72 Ha.	3.0	−16		N_2O, O_2
73 Br. R.	3.1	− 7¼		Pudendal block
74 Si.	2.5	− 1½		N_2O, O_2, Trilene

of this report to present data which indicate that hydrogen ion concentration has the important role of maintenance of adequate ventilation during the first 3 to 4 days of life.

METHOD OF STUDY

The patients in the first part of the study consisted of 51 healthy infants. From 37 of the 51 infants blood specimens were obtained whenever possible from the umbilical artery and vein at the time of birth; and from the temporal artery of each infant at 1, 4, 24, 48, 72, and 96 hours of life. Samples of venous blood were also obtained from the mothers of 14 infants at the time of delivery, and blood was drawn from the umbilical vein and artery of their infants at the time of birth. Subsequently capillary blood was obtained from these infants at 4 hours of age. The blood was analyzed for plasma pH, CO_2 content, protein, O_2 content and capacity, and hematocrit. The pCO_2 and buffer base were calculated from the Singer-Hastings nomogram.[2] Oxygen saturation was calculated from the oxygen content and capacity.

In a second series of 23 healthy infants, 3 to 135 hours old, blood was obtained from the temporal artery and analyzed for plasma pH, CO_2, O_2 content and capacity, and hematocrit, and whole blood pCO_2, and pO_2.

Sampling technique. The technique of Eastman[3a] was used for obtaining cord blood, with the following modification suggested by him.[3b] After partial delivery of the infant the cord was double clamped near the placenta. Five seconds was allowed to elapse and then double clamps were placed upon the cord near the umbilicus. The cord was cut between the paired clamps; the artery and vein were identified, and blood was obtained from each vessel by anaerobic technique. This method of clamping the cord permits filling of the umbilical artery by the infant.

The technique for obtaining blood from the temporal artery was the same as previously described by one of us.[4] The right temporal artery, a branch of the right carotid, was utilized in most instances because blood from it is most nearly representative of that which bathes the respiratory center. If crying occurred during the time blood was obtained, the specimen was discarded. If a baby cried prior to sampling, a period of time was allowed to elapse before the specimen was obtained. The minimum fasting period was 4 hours.

Controls. Chemical determinations of blood obtained from the femoral artery of adults served as controls.[4]

Chemical methods. The samples for pH and CO_2 were immediately immersed in an ice bath, in which they remained until delivery to the laboratory. Because the laboratory was located several miles from the patients, the average elapsed time between obtaining the specimens and performing the analyses was about 3 hours and was occasionally as long as 5 hours. The portions used for determination of CO_2 content were transferred under light mineral oil into Pyrex tubes, capped with Parafilm and centrifuged.

Plasma pH was determined at room temperature with the use of the Beckman pH meter, Model G with the hypodermic electrode, and was corrected to 38° C. by the factors of Rosenthal.[5]

Total CO_2 content was determined on 0.2 ml. of plasma by the manometric method of Van Slyke and Neill.[6]

In 24 instances CO_2 and O_2 tension were determined by the bubble equilibrium procedure of Riley.[7] Oxygen content and capacity were determined by the syringe gas analyzer method of Roughton and Scholander[8] using 40 c.mm. of blood, measured directly from the initial syringe. After the O_2 content was determined the blood was saturated with O_2 by drawing room air into the syringe and rotating it horizontally for 10 minutes. This procedure was repeated with fresh aliquots of air for another 10 minutes and a third time for 5 minutes. The ratio of blood to air was approximately 1:7.

The hematocrit technique was that of Strumia,[9] except that heparin rather than oxalate was used as an anticoagulant. Strumia found that the addition of heparin to the blood sample resulted in a somewhat higher value for the hematocrit than did the addition of double oxalate.

Plasma protein values were obtained by the gradient tube specific gravity procedure of Lowry and Hunter.[10]

All oxygen determinations and the majority of all of the other analyses were done in duplicate. Very infrequently analyses for pH and CO_2 were single determinations. Hematocrit values represent the average of 4 measurements.

Statistics. All statistical analyses were done by Mr. Edward Graham of the Department of Statistics, Temple University.

Clinical history. The selection of the infants for the study was determined on the basis of lack of serious prenatal disturbances, of no complications during delivery, and of a birth weight of 2.2 kilograms or more. Subsequently those infants who had any significant disturbance during their postnatal hospital course were eliminated from the study.

Sixty-seven of the mothers were well and 7 had some complication of pregnancy. Five of the latter 7 mothers had excessive weight gain without evidence of toxemia. Two Wassermann-fast mothers received a total of 10,000,000 units of procaine penicillin in the second trimester of pregnancy.

The duration of labor varied from ¼ to 15½ hours. Complete details of the analgesia and anesthesia used for delivery of each mother are presented in Table I and arranged in the same sequence to correspond with the chemical data in Table II and Table V. Forty-three mothers received no analgesia and 7 had no anesthesia. For those mothers who received one or more of the following drugs for analgesia, the dose was as follows: Demerol, 100 mg., scopolamine 0.4 mg., sodium Amytal 500 mg., or atropine 0.4 mg.

All infants were in vertex presentation and breathed spontaneously. There were only 2 instances in which complications were noted at delivery. Infant 27 Gr. had a persistent posterior presentation, manual rotation was not possible, and rotation by forceps was accomplished. Infant 33 Si. had a nuchal cord.

At birth all 74 infants of the 2 study groups were considered to be at full term as judged by birth weights which range from 2.3 to 3.9 kilograms, with an average weight of 3.1 kilograms.

All infants received prelacteal feedings. Those infants who were fed formulas were given 3 prelacteal feedings followed by a

10 calorie per ounce formula of evaporated milk and Dextri-Maltose. Only 3 of the 51 infants listed in Table II received a formula; the other 47 were breast fed.

RESULTS

The chemical values of the maternal and cord bloods at birth, and of the temporal artery blood at various times after birth for each infant are enumerated in Table II. Table III is a summary of the averages and range of chemical values for plasma pH, CO_2 content, bicarbonate ion (HCO_3^-), CO_2 tension, buffer base, hemocrit and oxygen saturation of the infants. The data for maternal venous blood are compared to similar data obtained from venous blood of healthy adult males; data for umbilical vein, umbilical artery, and temporal artery blood of the infants are compared to similar data obtained from femoral artery blood of healthy adult males.[4] The standard errors of the means and the significance have been computed. Statistical analyses of the chemical values for samples of blood from the umbilical artery and vein, respectively, are available for only 17 infants from whom we were successful in obtaining blood from the artery and the vein simultaneously. Capillary blood values at 4 hours of age are not included in the statistical analyses in Table III. Protein data are presented in Table V.

Plasma pH, (HCO_3^-), pCO_2. Fig. 1 is a composite representation of the average values for plasma pH, bicarbonate, pCO_2, and oxygen saturation for the purpose of showing the interrelationship of these values at birth and throughout the first 4 days of life.

An analysis of peripheral venous blood obtained from mothers at the time of delivery reveals average values for plasma bicarbonate, pCO_2, and pH of 18.6 mEq. per liter, 31.6 mm. Hg, and 7.39, respectively. The values for bicarbonate and pCO_2 of the mother are significantly lower than similar data obtained from normal adult males.[4] Unfortunately, neither these data nor other studies[12] of arterial blood indicate the type of acid-base abnormality, viz., whether the primary change is in the plasma bicarbonate or in the pCO_2. The problem has been previously discussed by many investigators and recently completely reviewed by Osterlund.[13]

Interpretation of the chemical values of the bloods from the 2 umbilical vessels is subject to definite limitations. (1) The umbilical vein carries blood from the placenta to the fetus where it is partially mixed with fetal blood. Thus the sample obtained from the umbilical vein represents blood from the placenta and not true arterial blood of the fetus. Blood obtained from the umbilical artery is from the aorta and is an admixture of umbilical vein blood and of blood from the 2 caval veins and the portal vein. James and co-workers[14] in a review of the work of Dawes and associates[15] very nicely demonstrated that umbilical artery blood is representative of arterial blood supplying fetal tissues. Arey[16] further noted that there is no difference in the quality of blood distributed to various parts of the body. (2) The fact that the cord is clamped near the placenta

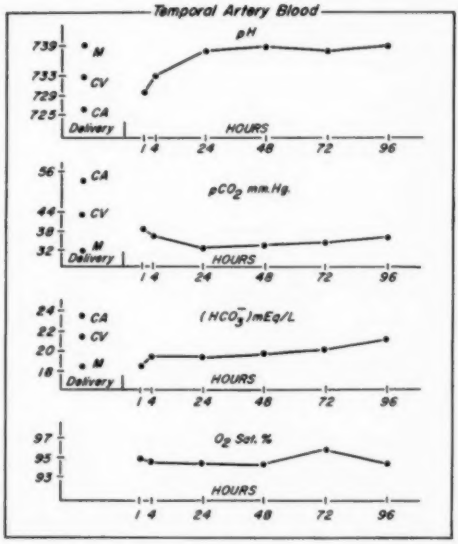

Fig. 1. Mean values for plasma pH, pCO_2, and (HCO_3^-) of mothers *(M)*, cord vein *(CV)*, and cord artery *(CA)* blood are shown at the time of delivery. Mean values of plasma pH, pCO_2, (HCO_3^-), and oxygen saturation obtained from analyses of temporal artery blood are indicated from 1 to 96 hours of age after delivery.

Table II. Chemical values of blood obtained from the mothers and from the cord at birth and from the temporal artery at various times after birth for each infant

Name	*Type of blood**	*Time (hours)*	*pH*	*CO_2 content (mEq./L.)*	*Bound CO_2 (HCO_3^-) (mEq./L.)*	*pCO_2 (mm. Hg)*	*O_2 Con. (vol. %)*	*O_2 Cap. (vol. %)*	*O_2 Sat. (%)*	*Hematocrit (mm./ml.)*
1 Bri.										
Cord	UV	Birth	7.37	24.1	22.8	40.4	18.3	22.9	79.9	66.8
Cord	UA	Birth	7.31	27.7	26.1	52.5	9.0	21.6	41.7	54.0
Infant	TA	1	7.27	20.5	19.2	42.9	25.1	26.5	94.8	64.1
Infant	TA	4	7.29							
Infant	TA	24	7.37	17.4	16.5	29.2	20.0	22.4	89.2	52.7
Infant	TA	48	7.34	22.3	21.1	39.9	22.7	24.6	92.3	56.9
Infant	TA	72	7.39	22.7	21.6	36.2				53.8
Infant	TA	96	7.42	19.6	18.7	29.2	21.5	22.3	96.4	53.4
2 Cu.										
Cord	UV	Birth	7.26	22.8	21.3	48.1				
Cord	UA	Birth	7.23	23.5	21.8	53.0				
Infant	TA	1	7.33	17.8	16.8	32.7				
Infant	TA	4	7.37	20.2	19.2	33.9				
Infant	TA	24	7.38	20.2	19.2	33.2				
Infant	TA	48	7.37	22.0	20.9	36.9				
Infant	TA	72	7.35	21.4	20.2	37.5				
Infant	TA	96	7.33	21.4	20.2	39.2				51.8
3. Do.										
Cord	UV	Birth	7.29	23.5	22.0	47.0	15.1	21.5	70.2	49.5
Cord	UA	Birth	7.19	26.4	24.4	65.2	3.2	22.1	14.4	51.2
Infant	TA	24	7.36	23.0	21.8	39.2	21.1	22.9	92.1	50.4
Infant	TA	48	7.31	22.1	20.8	42.2	21.1	21.8	96.8	48.5
Infant	TA	72	7.36	22.8	21.6	39.0				
Infant	TA	96	7.38	24.2	23.0	39.2				
4 Gre.										
Cord	UV	Birth	7.41	22.3	21.2	34.2				
Cord	UA	Birth	7.30	25.9	24.4	50.0				52.2
Infant	TA	4	7.42	21.8	20.8	32.5				58.5
Infant	TA	24	7.39	21.1	20.0	34.0	22.6	22.6	100.0	53.4
Infant	TA	48	7.43	15.1	14.4	22.4	23.0	25.0	92.0	53.7
Infant	TA	72	7.38	21.5	20.4	35.0	25.6	27.7	99.6	56.5
5 He.										
Cord	UV	Birth	7.30	22.9	21.5	44.2				
Cord	UA	Birth	7.29	24.5	23.0	48.3				
Infant	TA	1	7.30	22.5	21.2	43.6				
Infant	TA	4	7.34	21.4	20.2	38.3				
Infant	TA	24	7.44	21.3	20.3	30.8				
Infant	TA	48	7.43	18.9	18.0	27.8				59.6
Infant	TA	72	7.39	20.1	19.1	32.2	18.1	19.8	91.4	50.5
Infant	TA	96	7.37	22.2	21.0	37.0	17.3	18.9	91.5	47.1
Infant	TA	120	7.40	24.7	23.5	39.0	18.1	19.2	94.2	46.1
6 Ma.										
Cord	UV	Birth	7.37	22.4	21.2	37.5				
Cord	UA	Birth	7.35	23.2	21.9	40.5				
Infant	TA	1	7.33	20.3	19.1	37.2				
Infant	TA	4	7.36							
Infant	TA	24	7.37	21.7	20.6	36.0				
Infant	TA	48	7.39	22.5	21.4	36.0	20.0	20.7	96.8	46.7
Infant	TA	72	7.33	20.8	19.6	38.0	17.6	17.7	99.4	40.2
Infant	TA	96	7.42	21.9	20.9	32.9				
7 Sh.										
Cord	UV	Birth	7.32	23.9	22.5	44.4				

*Umbilical vein is designated as UV; umbilical artery blood as UA; temporal artery blood as TA; and capillary blood a CAP.

Table II—Cont'd

Name	Type of blood*	Time (hours)	pH	CO_2 content (mEq./L.)	Bound CO_2 (mEq./L.) (HCO_3^-)	pCO_2 (mm. Hg)	O_2 Con. (vol. %)	O_2 Cap. (vol. %)	O_2 Sat. (%)	Hematocrit (mm./ml.)
7—Cont'd										
Cord	UA	Birth	7.26	26.4	24.7	56.0				
Infant	TA	1	7.25	23.5	21.9	51.1				
Infant	TA	4	7.31	20.6	19.4	39.3				
Infant	TA	24	7.35							
Infant	TA	48	7.40	26.0	24.7	40.3				
Infant	TA	72	7.36	22.3	21.1	38.2	18.7	20.1	94.0	43.6
Infant	TA	96	7.39	21.5	20.4	34.4	17.0	18.0	94.4	41.8
8 St.										
Cord	UV	Birth	7.33	23.7	22.4	43.2				
Cord	UA	Birth	7.31	23.3	21.9	44.7				
Infant	TA	1	7.35	19.0	18.0	33.3				
Infant	TA	24	7.41	21.5	20.5	33.0				
Infant	TA	48	7.38	16.9	16.0	27.7				
Infant	TA	72	7.41	18.7	17.8	28.8				
9 Su.										
Cord	UV	Birth	7.27	23.0	21.5	47.7				
Cord	UA	Birth	7.24	26.7	24.9	58.8				
Infant	TA	1	7.24	18.6	17.3	41.2				
Infant	TA	24	7.36	18.4	17.4	31.7	20.3	21.2	95.9	
Infant	TA	48	7.36	20.5	19.4	35.1				
Infant	TA	72	7.41	21.3	20.3	32.8				
Infant	TA	96	7.41	23.8	22.7	36.3	20.7	21.4	96.7	49.7
10 Ta.										
Cord	UV	Birth	7.35	22.1	20.9	38.6				
Cord	UA	Birth	7.32	22.4	21.1	42.0				
Infant	TA	4	7.31	22.4	21.1	42.8				
Infant	TA	24	7.36	21.5	20.4	36.9				
Infant	TA	48	7.40	22.0	20.9	34.2				
Infant	TA	72	7.40	22.3	21.1	34.9				
Infant	TA	96	7.40	21.7	20.7	33.7	18.7	19.3	96.8	49.9
11 Va.										
Cord	UV	Birth								
Cord	UA	Birth	7.24	21.5	20.0	47.8				
Infant	TA	1	7.28	19.8	18.6	40.0	19.9	20.8	95.7	47.4
Infant	TA	4	7.29	20.2	18.9	40.3				
Infant	TA	24	7.44	21.5	20.5	31.0	18.3	19.6	93.3	45.5
Infant	TA	48	7.37							
Infant	TA	72	7.33	21.2	20.0	38.9	18.7	20.3	92.1	47.2
Infant	TA	96	7.36	22.7	21.5	38.7				
12 Ak.										
Cord	UA	Birth	7.22	25.3	23.5	59.0	4.5	18.4	24.4	44.7
Infant	TA	1	7.27	23.9	22.4	49.0	20.4	21.2	96.2	51.3
Infant	TA	4	7.26	22.3	20.8	47.5				54.5
Infant	TA	24	7.38	21.4	20.3	35.2				
Infant	TA	48	7.43	22.0	21.0	32.0	19.6	20.8	94.2	47.4
Infant	TA	72	7.39	22.2	21.1	35.5				
Infant	TA	96	7.44	24.9	23.8	35.5				
13 Be.										
Cord	UA	Birth	7.31	24.4	23.0	46.0				46.6
Infant	TA	1	7.33	20.2	19.0	37.1	21.6	22.0	98.2	53.7
Infant	TA	4	7.37	23.5	22.3	39.2				50.4
Infant	TA	24	7.42	22.7	21.6	33.9				47.5
Infant	TA	48	7.35	21.6	20.4	38.0	17.9	19.4	92.5	48.0
Infant	TA	72	7.38	21.0	19.9	34.3	17.7	17.9	99.0	39.3
Infant	TA	96	7.42	22.7	21.6	33.9				

Table II—Cont'd

Name	*Type of blood**	*Time (hours)*	*pH*	*CO_2 content (mEq./L.)*	*Bound CO_2 (mEq./L.) (HCO_3^-)*	*pCO_2 (mm. Hg)*	*O_2 Con. (vol. %)*	*O_2 Cap. (vol. %)*	*O_2 Sat. (%)*	*Hematocrit (mm./ml.)*
14 Br.										
Cord	UA	Birth	7.29	25.3	23.7	50.3				
Infant	TA	24	7.40	23.7	22.6	36.8				
Infant	TA	48	7.40	24.6	23.4	38.2	18.2	19.5	93.4	43.5
Infant	TA	72	7.43	23.4	22.3	34.4	18.8	19.6	95.9	45.6
Infant	TA	96	7.40	25.2	24.0	40.0	19.0	19.2	98.9	44.2
Infant	TA	120	7.38	25.0	23.7	40.5	16.7	17.8	93.8	38.8
Infant	TA	144	7.37	22.5	21.3	38.0				
15 Ed.										
Cord	UA	Birth	7.42	22.0	21.0	32.9				
Infant	TA	1	7.38	22.0	20.9	35.9	23.3	23.9	97.4	53.2
Infant	TA	24	7.40	23.6	22.5	36.8	22.0	23.5	93.6	50.5
Infant	TA	48	7.40	21.7	20.6	33.9				55.4
Infant	TA	72	7.41	21.4	20.4	32.9				
16 Ka.										
Cord	UA	Birth	7.31	19.2	18.1	36.7				
Infant	TA	24	7.34	19.5	18.4	34.9				
Infant	TA	48	7.39	22.2	21.1	35.0				
Infant	TA	72	7.45	23.8	22.8	33.0				
Infant	TA	96	7.36	22.8	21.6	39.2	20.6	22.0	93.7	50.1
Infant	TA	120	7.41	20.6	19.6	31.5	20.3	21.9	92.7	50.9
17 Ki.										
Cord	UA	Birth	7.44	20.0	19.1	28.7				
Infant	TA	1	7.33	21.2	20.0	39.0				
Infant	TA	4	7.37	20.4	19.3	34.2				
Infant	TA	24	7.40	19.2	18.3	30.0				
Infant	TA	48	7.42	23.1	22.0	34.3	19.6	20.6	95.2	47.9
Infant	TA	96	7.36	23.5	22.2	40.1	17.8	18.9	94.2	
Infant	TA	120	7.38	23.8	22.7	37.0				
18 Li.										
Cord	UA	Birth*	7.31	19.5	18.4	37.1	12.6	22.6	55.7	
Infant	TA	4	7.37	19.6	18.6	32.9				
Infant	TA	24	7.40	19.5	18.6	30.5				
Infant	TA	96	7.38	23.5	22.3	38.2				
19 McG.										
Cord	UA	Birth	7.11	24.2	22.0	70.0	3.4	18.5	18.3	44.2
Infant	TA	4	7.36	23.0	21.8	39.2				
Infant	TA	24					19.1	21.3	89.8	
20 Men.										
Cord	UA	Birth	7.35	20.0	18.9	35.0				
Infant	TA	1	7.31	17.3	16.3	33.0				
Infant	TA	24	7.40	19.2	18.3	30.1				
Infant	TA	48	7.39	17.7	16.8	28.2				
Infant	TA	72	7.40	19.9	18.9	31.0				
Infant	TA	96	7.39	19.2	18.2	30.9				
21 Mi.										
Cord	UA	Birth	7.19	27.4	25.3	67.7				
Infant	TA	24	7.35	22.7	21.5	39.5				
Infant	TA	48	7.41	22.7	21.6	34.5				
Infant	TA	72	7.34	19.3	18.2	34.5				
Infant	TA	96	7.46	21.5	20.6	29.8				
22 Wh.										
Cord	UA	Birth	7.20	23.8	22.0	58.0				
Infant	TA	1	7.31	16.5	15.5	31.5				

Table II—Cont'd

Name	Type of blood*	Time (hours)	pH	CO_2 content (mEq./L.)	Bound CO_2 (mEq./L.) (HCO_3^-)	pCO_2 (mm. Hg)	O_2 Con. (vol. %)	O_2 Cap. (vol. %)	O_2 Sat. (%)	Hematocrit (mm./ml.)
22—Cont'd										
Infant	TA	4	7.35	19.9	18.8	34.5	27.3	28.3	96.5	70.0
Infant	TA	24	7.39	20.6	19.6	33.0	25.1	25.3	99.3	60.0
Infant	TA	72	7.38	23.5	22.3	38.5				
Infant	TA	96	7.39	22.2	21.1	35.9				
23 Whi.										
Cord	UA	Birth	7.31	21.0	19.8	40.0				
Infant	TA	1	7.28	18.5	17.3	37.8	24.1	24.9	96.8	60.7
Infant	TA	4	7.28	19.2	18.0	39.0	25.8	26.9	95.9	63.5
Infant	TA	24	7.34	19.6	18.5	35.0	23.1	23.8	97.1	54.7
Infant	TA	48	7.34	19.1	18.0	34.9	22.7	23.4	97.0	53.1
Infant	TA	72	7.35	21.6	20.4	37.9				
Infant	TA	96	7.38	22.1	21.0	36.4				
Infant	TA	120	7.38	19.3	18.3	32.3				
24 Wi.										
Cord	UA	Birth	7.30	26.3	24.7	50.8	7.9	18.1	43.6	48.7
Infant	TA	24	7.38	22.8	21.6	37.1	21.5	22.6	95.1	47.1
Infant	TA	48	7.40	21.7	20.6	34.0	23.0	23.8	96.6	59.1
Infant	TA	72	7.40	18.7	17.8	29.3				
25 Wo.										
Cord	UA	Birth	7.21	20.2	18.7	48.0				
Infant	TA	1	7.21	17.9	16.6	42.3	22.4	24.8	90.3	54.3
Infant	TA	4					22.6	24.9	90.4	55.7
Infant	TA	24	7.35	23.6	22.3	41.5	21.4	22.1	96.8	51.7
Infant	TA	48	7.38	23.9	22.7	39.0	19.8	22.1	89.6	48.7
Infant	TA	72	7.42	25.6	24.4	38.2	18.9	21.3	88.7	48.4
26 Cr.										
Infant	TA	1	7.35	19.7	18.6	34.3				
Infant	TA	24	7.38	22.2	21.1	36.4	20.0	22.6	88.5	54.2
Infant	TA	48	7.34	18.5	17.5	33.2				
Infant	TA	72	7.37	20.3	19.2	34.1	22.4	23.7	94.5	54.3
Infant	TA	120					21.3	21.9	97.3	49.3
27 Gr.										
Infant	TA	1	7.28	20.1	18.8	41.0	24.4	26.0	93.8	59.8
Infant	TA	24	7.43	19.2	18.3	28.3	23.0	25.2	91.2	57.2
Infant	TA	48	7.42	23.1	22.0	34.5	22.9	25.0	91.6	56.3
Infant	TA	96					20.2	22.6	89.3	
Infant	TA	120	7.38	22.2	21.1	37.0				
Infant	TA	144	7.40	23.4	22.2	37.0	20.2	22.6	89.3	51.8
Infant	TA	168	7.38	25.1	23.8	42.0	15.3	21.4	71.5	51.1
28 Bro.										
Infant	TA	4	7.32	20.1	18.9	37.5				62.5
Infant	TA	24	7.38	16.0	15.2	26.4				
Infant	TA	48	7.35	23.5	22.2	41.0				
Infant	TA	72	7.43	22.0	21.0	32.3	22.3	23.3	95.7	51.3
29 Co.										
Infant	TA	4	7.33	21.5	20.3	39.5	24.1	25.5	94.5	65.2
Infant	TA	24	7.34	19.3	18.2	34.7				60.3
Infant	TA	48	7.38	18.0	17.0	30.0	23.3	24.3	95.8	58.5
Infant	TA	72	7.39	19.7	18.7	31.1	22.9	24.0	95.4	57.4
Infant	TA	96	7.32	23.0	21.7	42.9	22.6	23.4	96.5	58.2
30 Fu.										
Infant	TA	4	7.35	22.8	21.6	39.5	22.7	23.5	96.6	
Infant	TA	9	7.36	23.5	22.3	41.5	21.9	23.4	93.5	53.0

Table II—Cont'd

Name	*Type of blood**	*Time (hours)*	*pH*	*CO_2 content (mEq./L.)*	*Bound CO_2 (mEq./L.) (HCO_3^-)*	*pCO_2 (mm. Hg)*	*O_2 Con. (vol. %)*	*O_2 Cap. (vol. %)*	*O_2 Sat. (%)*	*Hematocrit (mm./ml.)*
30—Cont'd										
Infant	TA	24	7.43	22.9	21.9	33.4	20.6	22.7	90.7	58.5
Infant	TA	48	7.41	22.3	21.2	34.2				51.7
31 Ga.										
Infant	TA	4	7.31	21.2	19.9	40.4	19.3	21.4	89.9	56.0
Infant	TA	24	7.36	21.3	20.2	37.0	20.3	21.3	95.3	52.3
Infant	TA	48	7.44	23.6	22.5	33.9				52.5
Infant	TA	72	7.40	21.9	20.8	34.1	20.8	21.7	95.8	52.8
Infant	TA	96	7.39	24.7	23.5	39.1	20.0	21.3	93.8	51.4
32 Gra.										
Infant	TA	4	7.33	16.4	15.5	30.1	24.4	26.6	91.7	62.3
Infant	TA	24	7.35	17.1	16.2	30.1	24.4	25.7	87.2	53.4
Infant	TA	48	7.36	21.4	20.3	36.9				57.4
33 Si.										
Infant	TA	4	7.33	20.0	18.9	36.5	24.3	25.6	94.9	59.4
Infant	TA	72	7.38	20.2	19.2	33.0	23.1	23.8	97.1	53.0
Infant	TA	96	7.37	23.6	22.4	39.4	21.9	23.4	93.5	58.0
Infant	TA	120	7.39	22.2	20.0	36.0	19.5	20.0	97.5	49.4
34 Wy.										
Infant	TA	4	7.27	17.2	16.1	35.9	24.5	26.8	91.4	62.9
Infant	TA	24	7.38	18.2	17.3	29.9	25.8	26.8	96.4	60.4
Infant	TA	48	7.39	16.9	16.1	27.3	26.5	28.1	94.4	60.2
Infant	TA	120	7.37	17.0	16.1	28.8	23.8	25.4	93.7	55.3
35 Fo.										
Infant	TA	9	7.32	15.1	14.3	28.5	28.5	28.5	100.0	70.9
Infant	TA	24	7.40	13.6	12.9	21.5	24.9	25.1	99.2	58.5
Infant	TA	96	7.36	20.6	19.5	35.0	22.9	24.8	92.3	56.4
36 Me.										
Infant	TA	8	7.36	21.5	20.2	37.5	26.1	28.0	93.0	64.9
Infant	TA	24	7.38	21.2	20.1	34.7				59.3
Infant	TA	48	7.38	19.4	18.4	31.7				52.6
Infant	TA	72	7.40	23.9	22.7	37.1	23.9	24.8	96.3	58.4
Infant	TA	96	7.36	21.8	20.6	37.2	23.4	24.8	94.3	55.1
37 Wi.										
Infant	TA	48	7.42	19.1	18.2	28.7				52.6
Infant	TA	72	7.32	20.1	18.9	37.5	22.3	22.6	98.5	
Infant	TA	96								51.9
38 Wo.										
Mother	V	Birth	7.45	17.3	16.5	25.0				39.0
Cord	UV	Birth	7.34	22.1	21.0	40.0				57.6
Cord	UA	Birth	7.28	23.2	21.7	47.0				
39 Ro.										
Mother	V	Birth	7.34	21.2	20.1	38.0				
Cord	UV	Birth	7.28	24.8	23.2	50.0				
Cord	UA	Birth	7.12	29.3	27.0	84.5				
Infant	CAP	4	7.35	21.0	19.9	36.5				
40 Wo.										
Mother	V	Birth	7.49	16.3	15.7	21.0				34.5
Cord	UV	Birth	7.36	19.7	18.6	34.0				47.2
Cord	UA	Birth	7.31	22.6	21.3	43.0				47.4
Infant	CAP	4	7.33	20.6	19.3	37.8				
41 Pl.										
Mother	V	Birth	7.36	20.2	19.1	35.0				45.7
Cord	UV	Birth	7.33	24.3	22.9	44.5				46.8

Table II—Cont'd

Name	Type of blood*	Time (hours)	pH	CO_2 content (mEq./L.)	Bound CO_2 (mEq./L.) (HCO_3^-)	pCO_2 (mm. Hg)	O_2 Con. (vol. %)	O_2 Cap. (vol. %)	O_2 Sat. (%)	Hematocrit (mm./ml.)
41—Cont'd										
Cord	UA	Birth	7.26	23.1	21.6	49.5				42.1
Infant	CAP	4	7.33	19.7	18.5	35.9				
42 Qu.										
Mother	V	Birth	7.45	19.8	18.9	28.0				30.1
Cord	UV	Birth	7.29	22.6	21.2	44.9				39.5
Cord	UA	Birth	7.19	25.7	23.9	63.5				39.0
Infant	CAP	4	7.37	21.2	20.1	36.0				40.4
43 Rob.										
Mother	V	Birth	7.32	18.3	17.2	34.0				67.5
Cord	UV	Birth	7.33	17.7	16.7	32.4				
Infant	CAP	4	7.35	21.0	20.9	36.5				
44 Sp.										
Mother	V	Birth	7.42	20.4	19.4	31.0				
Cord	UV	Birth	7.25	25.4	23.8	55.0				
Cord	UA	Birth	7.26							
Infant	CAP	4	7.32	15.5	14.6	29.0				
45 Ca.										
Mother	V	Birth	7.37							
Cord	UV	Birth	7.16	20.2	18.6	54.0				
Cord	UA	Birth	7.11							
46 Di.										
Mother	V	Birth	7.37	21.7	20.6	36.0				
Cord	UV	Birth	7.34	23.6	22.2	42.0				
Cord	UA	Birth	7.25	26.2	24.4	57.0				
47 He.										
Mother	V	Birth	7.42	20.4	19.4	31.0				
Cord	UV	Birth	7.31	23.4	22.0	44.5				
Cord	UA	Birth	7.28	25.9	24.2	53.0				
48 Je.										
Mother	V	Birth	7.30	19 8	18.6	39.0				40.0
Cord	UV	Birth	7.25	23.6	22.0	51.0				51.5
Cord	UA	Birth								49.8
49 Col.										
Mother	V	Birth	7.37	19.3	18.3	32.5				
Cord	UV	Birth	7.35	20.2	19.1	35.0				52.4
50 Pai.										
Mother	V	Birth	7.39	22.3	21.2	36.0				
Cord	UV	Birth	7.37	24.7	23.4	41.0				
51 Wil.										
Infant	CAP	4	7.32	18.5	17.4	34.8				68.9

only after the head is delivered limits any interpretation of chemical values to the conditions prevailing at the exact time of clamping the cord. (3) The accurate rapid identification of the umbilical vein and arteries in the cord can only be performed by obtaining blood simultaneously from each of them. This is particularly true for infants suffering from asphyxia with subsequent alteration in the color of the blood and size of the vessels. Therefore, in this study, statistical analyses of chemical values were performed only on the 17 infants from whom we were successful in obtaining both types of blood. Mean chemical values of blood obtained from the umbilical vein indi-

Table III. Summary of blood values at birth and various times after birth and comparison to normal adult values (controls)

Chemical determination	*Number of patients*	*Blood*		*Time (hours)*	*Values*		*Average values of 13 adults (controls)**	*Standard error of the means*	*Significance*
		Source	*Type*		*Range*	*Average*			
pH	12	Mothers	V†	Delivery	7.30-7.49	7.39	7.36 (V)	0.016	N.S.
	17	Cord	UV	Delivery	7.26-7.41	7.33	7.41 (A)	0.010	0.001
	17	Cord	UA	Delivery	7.12-7.35	7.26		0.014	0.001
	18	Infant	TA	1	7.21-7.38	7.30		0.011	0.001
	22	Infant	TA	4	7.26-7.42	7.33		0.009	0.001
	34	Infant	TA	24	7.34-7.44	7.38		0.005	0.001
	32	Infant	TA	48	7.31-7.44	7.39		0.006	0.001
	29	Infant	TA	72	7.32-7.45	7.38		0.006	0.001
	24	Infant	TA	96	7.32-7.46	7.39		0.007	0.01
CO_2 content (mEq./L.)	11	Mothers	V	Delivery	16.3-22.3	19.6	26.7 (V)	0.534	0.001
	17	Cord	UV	Delivery	17.7-25.4	23.0	24.4 (A)	0.283	0.001
	17	Cord	UA	Delivery	19.2-29.3	25.1		0.485	N.S.
	18	Infants	TA	1	16.5-23.9	20.0		0.491	0.001
	20	Infants	TA	4	16.4-23.5	20.7		0.404	0.001
	33	Infants	TA	24	16.0-23.7	20.5		0.407	0.001
	31	Infants	TA	48	15.1-26.0	21.1		0.402	0.001
	29	Infants	TA	72	18.7-25.7	21.5		0.309	0.001
	24	Infants	TA	96	19.2-25.2	22.5		0.313	0.001
(HCO_3^-) (mEq./L.)	11	Mothers	V	Delivery	15.6-21.2	18.6	25.3 (V)	0.498	0.001
	17	Cord	UV	Delivery	18.6-23.2	21.6	23.3 (A)	0.259	0.001
	17	Cord	UA	Delivery	21.1-27.0	23.4		0.434	N.S.
	18	Infants	TA	1	15.5-22.4	18.8		0.463	0.001
	20	Infants	TA	4	15.5-22.3	19.5		0.387	0.001
	33	Infants	TA	24	12.9-77.6	19.5		0.389	0.001
	31	Infants	TA	48	14.4-24.7	20.0		0.434	0.001
	29	Infants	TA	72	17.8-24.4	20.4		0.295	0.001
	24	Infants	TA	96	18.2-24.0	21.4		0.301	0.001
pCO_2 (mm.Hg)	11	Mothers	V	Delivery	21.0-39.0	31.6	45.5 (V)	1.597	0.01
	17	Cord	UV	Delivery	34.0-55.0	42.7	37.4 (A)	1.131	0.001
	17	Cord	UA	Delivery	28.7-84.5	53.4		2.596	0.001
	18	Infants	TA	1	32.7-57.1	39.1		1.288	N.S.
	20	Infants	TA	4	30.1-47.5	37.7		0.890	N.S.
	33	Infants	TA	24	21.5-41.5	33.4		0.709	0.001
	31	Infants	TA	48	22.4-42.2	34.1		0.816	0.001
	29	Infants	TA	72	28.8-39.0	34.8		0.539	0.001
	24	Infants	TA	96	29.2-42.9	36.4		0.708	N.S.
Buffer base (mEq./L.)	12	Mothers	V	Delivery	40.0-44.0	42.2	46.6 (V)	0.3217	0.001
	17	Cord	UV	Delivery	42.0-49.0	44.2	46.9 (A)	0.4308	0.001
	17	Cord	UA	Delivery	42.0-48.0	43.8		0.3951	0.001
	19	Infants	TA	1	38.0-44.0	42.3		0.4261	0.001
	20	Infants	TA	4	41.0-48.0	44.3		0.3776	0.001
	33	Infants	TA	24	41.5-48.5	44.7		0.3167	0.001
	31	Infants	TA	48	42.0-48.0	45.0		0.3419	0.001
	30	Infants	TA	72	42.0-49.0	44.8		0.3379	0.001
	23	Infants	TA	96	43.0-48.5	46.0		0.5302	N.S.
O_2 Sat. (%)	8	Infants	TA	1	90.3-98.2	95.0		0.881	
	9	Infants	TA	4	89.9-96.6	94.0		0.894	
	18	Infants	TA	24	87.2-100.0	94.0		0.924	
	14	Infants	TA	48	89.6-97.0	94.0		0.629	
	15	Infants	TA	72	88.7-99.6	96.0		0.801	
	14	Infants	TA	96	89.3-98.9	95.0		0.664	

*Chemical determinations of blood from femoral artery and antecubital vein of adults as previously published.[4]
†Peripheral vein.

Table III—Cont'd

Chemical determination	Number of patients	Blood		Time (hours)	Values		Average values of 13 adults (controls)*	Standard error of the means	Significance
		Source	Type		Range	Average			
Hematocrit (mm./ml.)	10	Cord	UV	Delivery	39.5-66.8	50.3		2.393	
	11	Cord	UA	Delivery	39.0-54.0	48.5		1.473	
	8	Infants	TA	1	47.4-64.1	55.6		1.949	
	12	Infants	TA	4	50.4-70.0	60.1		1.554	
	19	Infants	TA	24	45.5-60.3	54.1		1.073	
	20	Infants	TA	48	43.5-60.2	52.5		1.051	
	17	Infants	TA	72	39.3-58.4	49.7		1.483	
	15	Infants	TA	96	41.8-58.2	50.7		1.358	

cate a mild uncompensated metabolic acidosis. This is apparent by examination of the average values for plasma pH (7.33), bicarbonate content (21.6 mEq. per liter), and plasma pCO_2 (42.7 mm. Hg). Mean values of umbilical artery blood reveal a plasma pH of 7.26 associated with a normal bicarbonate content (23.4 mEq. per liter); these values in conjunction with an increased pCO_2 (53.4 mm. Hg) are indicative of respiratory acidosis. These data may be compared to the results of previous investigations (17 to 26) shown in Table IV.

One hour after birth the mean values of temporal artery blood for pH, bicarbonate, and pCO_2 are, respectively, 7.30, 18.8 mEq. per liter, and 39.1 mm. Hg. Thus, the majority of infants have an uncompensated metabolic acidosis, and about 10 per cent of them also have a respiratory acidosis as evidenced by the data in Table II.

The plasma pH at 4 hours of age, although significantly below the average level for adults, has increased to a mean value of 7.33. This increase, although small, appears to be highly significant as evidenced by an increase in the pH value for each infant from 1 to 4 hours of age. The change in pH is dependent upon a slight increase in the concentration of bicarbonate and upon a decrease in pCO_2. The chemical pattern continues to be that of an uncompensated metabolic acidosis.

By 24 hours of age, the increase in the mean value for pH to 7.38 has apparently been accomplished by a decrease in the mean plasma pCO_2 value to 33.4 mm. Hg (Table III). The mean value for bicarbonate remains relatively constant, although individual values exhibit the greatest variability of any period of the study. Sixty-two per cent of the infants had either a pH of 7.40 ± 0.02 or an elevated pH 7.45 ± 0.02 by 24 hours of age with a mean value for pCO_2 of 32.7 mm. Hg. Thirty-eight per cent of the infants had a pH less than 7.38 and a mean value for pCO_2 of 35.8 mm. Hg. Thus a normal or elevated plasma pH is related to a marked decrease in plasma pCO_2. The chemical pattern in the majority of infants at 24 hours of age is that of a partially compensated metabolic acidosis, although 4 infants in this age period had a respiratory alkalosis as indicated by a pH of 7.45 ± 0.02, and a low pCO_2. The increase in pH to 7.45 ± 0.02 in 4 infants is unexplained but may be due to (1) overcompensation of the metabolic acidosis or (2) the result of an attempt to increase ventilation because of inadequacy of the lung in respect to uptake of oxygen.

The mean values for pH, CO_2, and pCO_2 of temporal artery blood in the first 24 hours differ only slightly from similar studies of capillary blood reported by Graham and Wilson[27] and are identical with the data of Weisbrot and colleagues[12] which were obtained from chemical analysis of blood from the left atrium.

From 48 to 72 hours of age the mean values for plasma pH, pCO_2, and bicarbonate remain fairly constant with only

Table IV. Chemical values of umbilical vein and artery blood reported by various investigators

Authors	*Umbilical vein*			*Umbilical artery*		
	pH	*CO_2* (mEq./L.)*	*pCO_2 (mm. Hg)*	*pH*	*CO_2* (mEq./L.)*	*pCO_2 (mm. Hg)*
Ylppö[17]	7.02 (mixed blood obtained from umbilical vein and arteries)					
Bell et al.[18]	7.15	16.9		7.02	17.9	
Siedentopf and Eissner[19] (samples from pulsating cord)	7.37					
Eastman[20]	7.30	19.5	38.8	7.24	21.7	
Noguchi[21]	7.35	17.9	33.8	7.32	19.4	39.5
Overman, Etteldorf, Bass, and Horn[22]				7.39	22.8	
Kaiser†[23]	7.32			7.26		
Beer, Bartels, and Raczowski[24]	7.32	18.3	44.9	7.24	21.4	60.4
Weisbrot et al.[12]				7.23	25.0	58.4
MacKinney, Goldberg, Ehrlich, and Freymann[25]	7.28	19.1	48.5		20.6	
Vedra[26]	7.46	22.6			23.3	
Reardon, Baumann, and Haddad (present study)	7.33	23.0	42.7	7.26	25.1	53.4

*CO_2 is expressed as CO_2 content or combining power depending upon technique used by the authors. Figures converted from volumes per cent to mEq./L. for comparative purposes.

†Cesarean section.

Table V. Relationship of whole blood buffer base* to average values for plasma bicarbonate, protein, and hematocrit

Blood		*Time in hours*	*Buffer base (mEq./L.) average*	*(HCO_3^-) (mEq./L.) average*	*Protein (Gm. %) average*	*Hematocrit (ml. %) average*
Source	*Type*					
Cord	UV	Delivery	44.2	21.7	5.51	50.3
Cord	UA	Delivery	43.8	23.4	5.51	48.5
Infants	TA	1	42.3	18.8	5.68	55.6
Infants	TA	4	44.3	19.5	5.59	60.1
Infants	TA	24	44.7	19.5	5.59	54.1
Infants	TA	48	45.0	20.0	5.51	52.5
Infants	TA	72	44.8	20.4	5.59	49.7
Infants	TA	96	46.0	21.4	5.43	50.7

*Calculated from the Singer-Hastings nomogram.[2]

Values for buffer base are uncorrected for oxygen saturation.

slight daily variations. By 96 hours of age the major changes are in the plasma bicarbonate and pCO_2 values, each of which has increased appreciably, the mean values for pCO_2 being no different from that of the adult controls. Analyses of individual values reveal that all infants were able to raise their pH to 7.40 ± 0.02* at some time during the first 4 days of life. Of the 38 per cent of infants who had a plasma pH less than 7.38 by 24 hours of age, ¾ developed a pH of 7.40 ± 0.02 by 48 hours and the remainder by 72 to 96 hours of age. Although inspection of the range of values for pH (Table III) reveals that a value as low as 7.31 might be expected in some infants within 48 to 96 hours of life, this was uncommon and unexplained. Likewise an elevation of pH was uncommon; 7 infants had a pH of 7.45 ± 0.02 between 48 and 96 hours of age.

Thus under the conditions of this study, about 60 per cent of breastfed, well, noncrying, full-term infants had a chemical pattern of a metabolic acidosis partially compensated by hyperventilation (decreased

*Normal value in adults for arterial blood is 7.40.

pCO_2) between the fourth and twenty-fourth hours of life. About 40 per cent of these infants continued to have an uncompensated metabolic acidosis with correction of it usually being attained by the fourth day of life. Approximately one third of all infants had respiratory alkalosis at some time in the first 4 days of life. The data confirm previous observations that the majority of full-term infants exist in a state of acidosis.[12, 17, 22, 27-34]

Whole blood buffer base, hematocrit, and plasma protein. Buffer base (synonym "buffer anions") is bicarbonate ions (HCO_3^-) and nonbicarbonate buffer anions (Buf^-). Nonbicarbonate buffer anions consist of anions of hemoglobin, plasma proteins, organic phosphate of red cells, and small quantities of other buffers.[35] From the direct determination of pH, CO_2 content, hematocrit, and oxygen it is possible to calculate whole blood (buffer base) in adults from the Singer-Hastings nomogram.[2] Since the hemoglobin of the newborn differs in certain respects from that of adults, the participation of hemoglobin in changes of buffer base may not be of the same magnitude in both age groups. With this possible limitation, the data in Table III reveal that a slight deficit of buffer base in umbilical artery blood at the time of delivery becomes more severe at 1 hour of age after which there is progressive improvement to 96 hours of life.

The potential buffering capacity of the high hematocrit noted during the first few hours of life appears to be the reason that the deficit of buffer base is not greater than is actually noted in Table III. For example, (Table V) if at 1 hour of age the mean value for hematocrit of newborn infants was similar to the usual value of adults (45 ml. per cent), the mean value for buffer base would be 40 instead of 42 mEq. per liter. On the other hand, the slight increase in buffer base at 4 hours as compared to 1 hour of age is not all due to the concomitant increase in hematocrit. Part of the increase in buffer base in this time period is due to an increase in bicarbonate ion (Table V). From 48 to 96 hours the increase in buffer base is related to the increasing bicarbonate whereas the plasma protein remains relatively constant and the hematocrit is decreasing. Mean values for hematocrit both at 24 and 72 hours of age are significantly lower ($p < 0.01$) than the mean value for 4 hours of age.

Oxygen saturation. At 1 and 4 hours of age, the values for oxygen saturation (Table III) revealed a range from 90.3 to 98.2 per cent with the average values being between 94 and 95 per cent at each time. Thereafter the range was greater but the same average values persisted throughout the first 4 days of life.

Although the values for O_2 saturation of arterial blood were not very low and were associated with high hematocrit values, measurements of O_2 saturation do not necessarily reflect the amount of O_2 available to the tissues of newborn infants. Factors which influence O_2 dissociation from hemoglobin are variations in temperature, the type of hemoglobin, and the level of the pH.

Oxygen tension (pO_2). Since measurements of pO_2 are a more sensitive index of available oxygen than are determinations of oxygen saturation, temporal artery blood was obtained from an additional 23 well, newborn infants ranging in age from 3 to 135 hours, and analyzed for pO_2, pH, pCO_2, oxygen content and capacity and hematocrit. Oxygen saturation was calculated. The data for these infants are listed in Table VI. In Fig. 2 values for oxygen tension (pO_2) and oxygen saturation are plotted against the hemoglobin dissociation curves without regard to pH. Oxygen tension was relatively low in all infants; 20 of the values ranged from 75 to 99.9 mm. Hg, with a mean value of 84.4 mm. Hg.* The range of values for oxygen saturation was 88.1 to 100 per cent with a mean value of 94.3 per cent. In 2 infants values for pO_2 were 65.1 and 62.4 mm. Hg; the oxygen saturations were 89.8 and 93.2 per cent, respectively, and within the range of the oxygen saturations of the

*This value is 10 mm. Hg higher than mean values for pO_2 reported in a recent study by Graham.[36]

Table VI. Chemical values for pO_2, O_2 saturation,* pCO_2, pH, and hematocrit of blood from the temporary artery of full-term infants.

Name	*Gestation period (weeks)*	*Temp. (°F.)*	*Birth Weight (kilograms)*	*Age (hours)*	*pO_2 (mm. Hg)*	*O_2 saturation* (%)*	*pH*	*pCO_2 plasma (mm. Hg) (calculated)*	*pCO_2 whole blood (mm. Hg) (direct)*	*Hematocrit (c.c./100 c.c.)*
52 Es.	40	97	2.8	3	88.4	92.9	7.40			64.3
53 Mo.	40	96	3.2	6	77.6	88.1	7.33	32.8	37.0	52.9
54 Med.	39	96[3]	3.0	8	89.2	95.3				
55 Vau.	40		3.0	8	85.9	96.7				
56 Mar.	40		3.1	8	82.6	96.1				
57 Pa.	40	96[2]	3.1	10	88.3	94.2	7.35	34.9	38.0	55.4
56 Mar.	40		3.1	30	76.8	93.3	7.38	37.6		
58 Mat.	40	98	3.9	36	75.4	94.6	7.39	25.8		57.0
59 Al.	40	98[4]	2.8	39	94.7	100.0	7.39	29.1	32.0	58.4
60 Ge.	41	98[4]	2.9	45	86.3	98.0	7.39	31.1	31.0	53.0
61 Po.	40	98[6]	3.1	44	77.1	96.6	7.38	33.8	32.6	55.6
62 Ta.	40		2.8	57	78.8	91.5	7.44	28.8	30.5	59.3
63 Co.	40	98	3.0	59	77.2	92.9	7.39			
64 Car.	40		3.9	76	76.7	90.1	7.39	33.5		
65 Br. J.	40	100	2.9	85	84.6	96.3	7.36	36.0	34.1	51.7
66 La.	40	99	3.4	94	99.9	96.5	7.35	39.0	35.6	65.2
67 Law.	40	100	3.4	96	91.0		7.39	30.8	27.3	53.6
68 Gr.	40	98	3.3	99	88.3	90.1	7.36	41.3	38.1	53.8
69 De.	40	98[2]	3.2	102	82.8	93.2	7.42	34.3	36.8	60.2
70 Sm.	40	99	2.9	107	92.9	94.7	7.36	38.3	38.5	53.4
71 Col.	40	98[3]	3.6	117	83.7	95.8	7.33	41.8	43.5	60.1
72 Ha.	40	99	3.0	120	78.3		7.38	32.5	32.0	47.5
73 Br. R.	40	97	3.1	33	62.4	93.2	7.41	28.8	31.8	35.2
74 Si.	37	98	2.5	135	65.1	89.8	7.34	38.8 (H)	39.0	34.6

*O_2 saturation calculated from oxygen content and oxygen capacity.

Table VII. Chemical values of temporal artery blood of full-term infants at one and 48 hours of age and of premature infants at 48 hours of age

	Full-term 1 hour	*Premature*	*Full-term 48 hours*	*Significance*
pH	7.30	7.31	7.39	0.001
CO_2 mEq./L.	20.0	20.3	21.1	N.S.
(HCO^-_3) mEq./L.	18.8	19.4	20.0	N.S.
pCO_2 mm. Hg	39.1	38.9	34.1	0.001

other infants. One was an infant of 37 weeks' gestation with a birth weight of 2.5 kilograms; the other was a full-term infant delivered of an allegedly Wassermann-fast mother who was treated for syphilis during this pregnancy. Both of these infants also had a low hematocrit (less than 40). Although a larger series of infants should be studied with other techniques, these data indicate that in well full-term infants oxygen tension is not usually within the range which would be expected to excite the chemoreceptor reflexes of adults.

In Table VI pCO_2 values for 17 infants are listed in 2 columns: the first contains pCO_2 values calculated from the plasma pH and the CO_2 content, and the second, pCO_2 values obtained by direct measurements. The mean value for the calculated pCO_2 was 34.4 as compared to a value of 34.8 mm. Hg by direct measurement. These data offer further confirmation of the fact that

regardless of the method used,* pCO_2 is decreased in the majority of infants in the first few days of life.

DISCUSSION

Chemical studies of blood obtained from the umbilical artery (arterial blood of the fetus) reveal that the mild acidosis present in newborn infants at the time of birth is of both metabolic and respiratory origins. The metabolic acidosis is not associated with a decrease in the bicarbonate or CO_2 content but rather with a decrease of the nonbicarbonate buffer anions. This decrease in buffer anions (buffer base) is due either to an excess or fixed acids or to a deficit of base. The reason for an increased plasma pCO_2 at the time of birth is not apparent but may be due to the constant production of CO_2 at a time when the lung is nonfunctioning and the placental circulation has been interrupted.

Within an hour after birth, in the majority of infants there is no longer evidence of respiratory acidosis but the metabolic acidosis is of greater magnitude than is noted at birth and is associated with a decrease in both the bicarbonate and nonbicarbonate buffer anions. The normal mean value for plasma pCO_2 (39 mm. Hg) indicates that alveolar ventilation is adequate for infants at 1 hour of age, since pCO_2 of arterial blood reflects the alveolar pCO_2 of the lung. However, plasma pH is decreased because infants at this age apparently do not have the ability to compensate for a metabolic acidosis by hyperventilation.

Between 4 and 24 hours of age, the infants are either hyperventilating or CO_2 production is diminished as evidenced by the marked decrease in arterial pCO_2. We suggest that this change in pCO_2 is on a ventilatory basis. In about 18 per cent of the infants the primary metabolic acidosis is converted into respiratory alkalosis.

Correction of the metabolic acidosis is initiated in breast-fed infants about the fourth day of life by an increase in bicarbonate, and further improvement in plasma pH. These chemical data differ from those

*The two methods do not agree as closely as might be desired. The direct measurement of pCO_2 is faster and less tedious, but the indirect method appears to be more reliable in our laboratory.

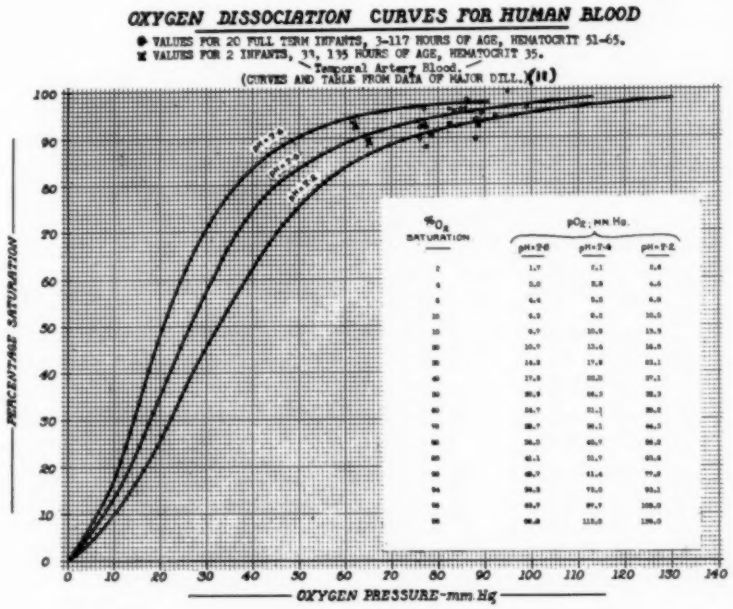
OXYGEN DISSOCIATION CURVES FOR HUMAN BLOOD
● VALUES FOR 20 FULL TERM INFANTS, 3-117 HOURS OF AGE, HEMATOCRIT 51-65.
✖ VALUES FOR 2 INFANTS, 31, 135 HOURS OF AGE, HEMATOCRIT 35.
Temporal Artery Blood.
(CURVES AND TABLE FROM DATA OF MAJOR DILL.)(11)
PERCENTAGE SATURATION
OXYGEN PRESSURE-mm Hg
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
0 10 20 30 40 50 60 70 80 90 100
pH=7.6
pH=7.4
pH=7.2
% O2 SATURATION
pO2 : MM Hg.
pH=7.6
pH=7.4
pH=7.2

Fig. 2.

of well premature infants[4] who have the same values for plasma pH, CO_2 content, and pCO_2 at 2 to 3 days of age, as do full-term infants at 1 hour after birth (Table VII).

The facts, that pCO_2 is markedly decreased and that pO_2 is not within the range which would be expected to excite the chemoreceptor reflexes, would suggest the concept that plasma pH is the major chemical stimulus to respiration from 4 hours after birth through the first 3 days of life. This concept differs from that of Weisbrot and associates[12] and of Graham and Wilson[27] both of whom limited their studies to the first 24 hours of life. Weisbrot and coworkers[12] postulate that "the low pCO_2 represents the end results of the respiratory center's effort to attain a level of pCO_2 similar to that to which it has been exposed in utero." Graham and Wilson[27] suggest that the changes in pH, pCO_2, and calculated oxygen tension, indicate "that a considerable portion of the total stimulus to respiration is derived from the effect of oxygen lack."

If the hypothesis that hydrogen ion concentration regulates respiration in the newborn is accepted, certain additional concepts may be considered:

(1) If the respiratory centers or chemoreceptors are sensitive to changes in hydrogen ion concentration after birth, this sensitivity is presumably present at the moment of birth. Thus, the hydrogen ion concentration may be an important stimulus for initiation of respiration. Moreover, extreme changes in fetal plasma pH as well as in pCO_2 or pO_2 may damage the respiratory centers so that they are incapable of response at the time of birth.

(2) The maintenance of the normal hydrogen ion concentration within the first hours after birth depends upon the ability of the lung to ventilate and internal shifts in acid-base equilibrium rather than upon combined respiratory and renal functions. The ability of the fasting full-term infant to maintain a fairly stable hydrogen ion concentration for at least 2 to 3 days after birth without much renal participation* may be one reason why infants in this age range do not display clinical evidence of diseases which are related to primary renal insufficiency. On the other hand, if the lung does not have the capacity for adequate ventilation as the result of cardiac, central nervous system, or pulmonary difficulties, the effect may be a severe uncompensated metabolic acidosis and in very severe disturbances there would be clinical evidence of respiratory distress with superimposed respiratory acidosis and anoxia. The net result might be death or cerebral damage due to both anoxia and acidosis. Certainly infants who have limited pulmonary function as indicated by an uncompensated metabolic acidosis have a very narrow margin of safety in any situation which disturbs the acid-base balance.

CONCLUSIONS

Analyses of data related to the 3 chemical stimuli to respiratory activity, pH, pCO_2, and pO_2 in temporal artery blood of healthy full-term infants at various ages after birth indicate that:

1. Metabolic and respiratory acidosis are present at birth. Respiratory acidosis is usually corrected by the fourth hour of life. Metabolic acidosis is partially corrected in the majority of breast-fed infants in the first 24 hours of age by a slight elevation in bicarbonate, and buffer anions of hemoglobin, and a marked decrease in pCO_2; long-term correction over 4 days is apparently accomplished by an increase in bicarbonate.

2. During at least the first 3 days of life the plasma hydrogen ion concentration may be the important chemical stimulus to respiratory ventilation.

3. Cognizance of the chemical variations in healthy infants during this early age period is necessary for evaluation of sick infants.

*This is not meant to imply that renal function is either adequate or inadequate in the newborn but renal participation in the regulation of acid-base balance in 2 to 3 day fasting infants is certainly minimal.

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Electrocardiographic evaluation of pulmonic stenosis

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PATIENTS with pulmonic stenosis and intact cardiac septa may have similar symptoms and physical and radiologic findings despite marked differences in severity of the stenosis. This fact poses a problem in selection of patients for cardiac catheterization and surgery and in evaluation of effects of surgical treatment.

If patients with physical signs of pulmonic stenosis present with symptoms of breathlessness and fatigue on exertion, or with cyanosis, or have marked enlargement of the right heart chambers, or signs of right-sided heart failure, then there is little problem in recognizing that the stenosis is marked. Such an extreme picture is fortunately not the usual one in this common malformation. For the patients with lesser manifestations, there may be uncertainty in assessing the degree of stenosis on clinical grounds.

Symptoms are usually absent in patients with mild obstruction but may also be lacking even with quite severe stenosis. Two of the highest right ventricular pressures cited in the study to be presented were recorded in patients considered by their parents to be essentially symptom free. One, a 21-year-old concert pianist, had a pressure of 240/23 mm. Hg in the right ventricle and the other, a 5½-year-old boy, had a measurement of 220/13 mm. Hg. Included in Blount's[1] review of asymptomatic isolated valvular pulmonic stenosis was a case in which the pressure was 183 mm. Hg in the right ventricle. While these examples are unusual, it is true that patients born with a cardiac anomaly may have difficulty in assessing their limitations when they have not known what it is like to feel "normal." Often it is only in retrospect after a successful operation that they realize disabilities which they had previously minimized or ignored.

Although cyanosis is found only in those patients with marked stenosis, most of them cannot manifest cyanosis since a venous-

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arterial shunt in this condition depends on patency of the foramen ovale or a defect in the atrial septum. In most such patients, just as in the normal population, the foramen ovale is sealed and there is no atrial septal defect. For example in the present study, 10 patients with severe stenosis had cyanosis, but in 15 others, with equally elevated right ventricular systolic pressures of 150 mm. Hg or more, the arterial oxyhemoglobin saturation was within normal limits.

The lack of a precise correlation between cardiac size and severity of stenosis is indicated in Figs. 1, 2, and 3. In 2 patients with pulmonic stenosis but without cardiac enlargement and without symptoms (Fig. 1) the right ventricular pressure in one was only 36/4 mm. Hg at rest, rising to 56/4 on exercise. In contrast, the second patient had a pressure in the right ventricle of 158/8 mm. Hg at rest and, on exercise, a rise to 195/11.[2]

The 4 patients with slight cardiac enlargement (Fig. 2) illustrate the range of stenosis from insignificant (R.V. 38/3 mm. Hg) to extreme (R.V. 196/7 mm. Hg). More marked cardiac enlargement (Fig. 3) was associated with moderate or severe obstruction, but these patients similarly had a wide range of systolic pressures in the right ventricle, from about 100 to over 200 mm. Hg.

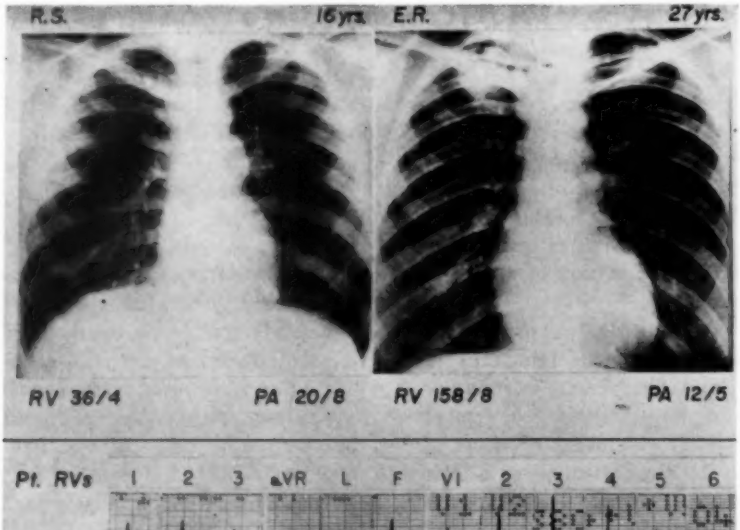
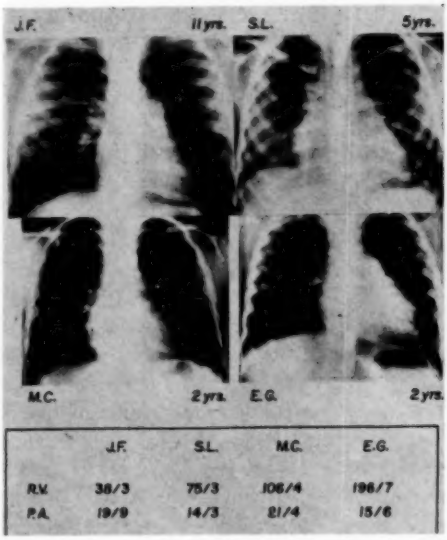


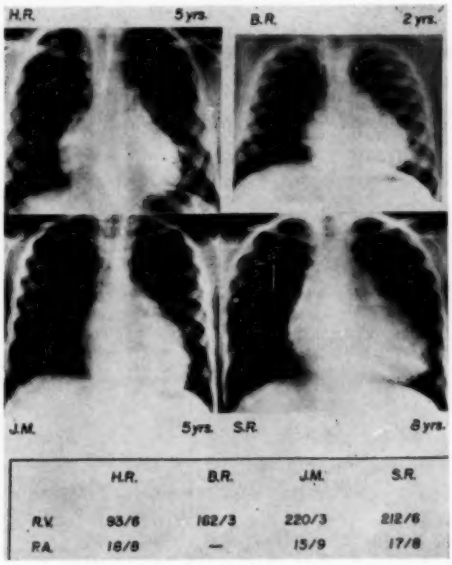
Fig. 1. Absence of cardiac enlargement in patients R. S. with mild pulmonic stenosis and E. R. with severe stenosis. Pressures at cardiac catheterization appear below corresponding x-ray. *RVs* in legend alongside electrocardiogram refers to right ventricular systolic pressure in this figure and Figs. 4 and 5.

Note that patient R. S. shows no axis deviation, normal left ventricular dominance, and an rsr′ pattern in V_1, while patient E. R. shows right axis deviation and evidence of right auricular enlargement, right ventricular hypertrophy and "strain."



	J.F.	S.L.	M.C.	E.G.
R.V.	38/3	75/3	106/4	196/7
P.A.	19/9	14/3	21/4	15/6

Fig. 2. Slight cardiac enlargement in 4 patients with right ventricular systolic pressures ranging from 38 to 196 mm. Hg.



	H.R.	B.R.	J.M.	S.R.
R.V.	93/6	162/3	220/3	212/6
P.A.	18/8	—	15/9	17/8

Fig. 3. Marked cardiac enlargement in patients with moderate to severe pulmonic stenosis (*RVs* 96 to 220 mm. Hg).

Electrocardiograms taken close to the time of x-rays and catheterization in these 10 patients are illustrated in Figs. 1, 4, and 5. They demonstrate the range of patterns from simple conduction disturbance to pronounced hypertrophy associated with myocardial damage and dilatation of the right ventricle. These electrocardiographic changes afforded a better index of the severity of the pulmonic stenosis than did the other observations prior to cardiac catheterization.

A study was therefore undertaken, in both unoperated and postoperative patients, to determine whether the electrocardiograms consistently reflected the burden on the right ventricle in this malformation.

PLAN OF STUDY

Electrocardiograms recorded close to the time of pressure measurements at cardiac catheterization and/or operation were analyzed in 73 cases of pulmonic stenosis, intact ventricular septum, and no left-to-right shunt. In general, there was good agreement between pressures measured at rest during catheterization and those obtained in the operating room. Two patients, both cyanotic and with severe stenosis, did not have catheterization prior to operation; for them the values obtained at operation were used. Records of 4 other autopsied patients who died because of extreme, unrelieved stenosis were also analyzed. Included in the tabulation are 10 postoperative patients who still had a systolic gradient of 5 mm. Hg or more between the right ventricle and pulmonary artery at recatheterization. Pure infundibular stenosis was proved in 4 patients at operation or at autopsy; it is suspected in another who has not yet been operated upon. In the remaining patients the obstruction was valvular, although in some of the most severe cases, associated infundibular stenosis due to muscular hypertrophy was detected at operation or at autopsy.[2]

Electrocardiograms were recorded with the patient supine and with attention to prevent "smearing" of precordial positions. Records on patients in the pediatric age

group were taken by one technician and recorded on a direct-writing instrument (Sanborn Cardioscope). Records on the adults were photographic electrocardiographs obtained with a Cambridge string galvanometer. Amplitude of the deflections as reported was corrected so that a deflection of 1 millimeter was equivalent to 1 millivolt.

The distribution of the patients by age is shown in Table I.

From the literature, an analysis was made of electrocardiograms that were reproduced and accompanied by pressure measurements. Forty-one of these were sufficiently complete to be included in Fig. 6.[1, 3-11] The findings were similar to those obtained in our studies.

The level of systolic pressure in the right ventricle was taken as the indicator of severity of stenosis. In Fig. 6 these pressures are ranked in increments of 10 mm. from the lowest to the highest, and the number of patients at each pressure level is recorded in the first column. In the other columns are tabulated the number of patients at each level who demonstrated that particular electrocardiographic finding. Thus the results are presented as a scattergram, with the patients from The New York Hospital represented by closed circles and those from the literature by open circles.

RESULTS

Separate aspects of the electrocardiogram were analyzed and correlated with the systolic pressure in the right ventricle. There was a significant correlation between the pressure level and (1) the amplitude of the R wave in V_1; (2) the amplitude of the S wave in V_6; (3) high, peaked P_2; (4) leftward spread of precordial T wave inversion; and (5) leftward displacement of the transitional zone. The correlation coefficients are shown in Table II. Perfect correlation would be indicated by the number 1.0.[12] The values obtained indicate that

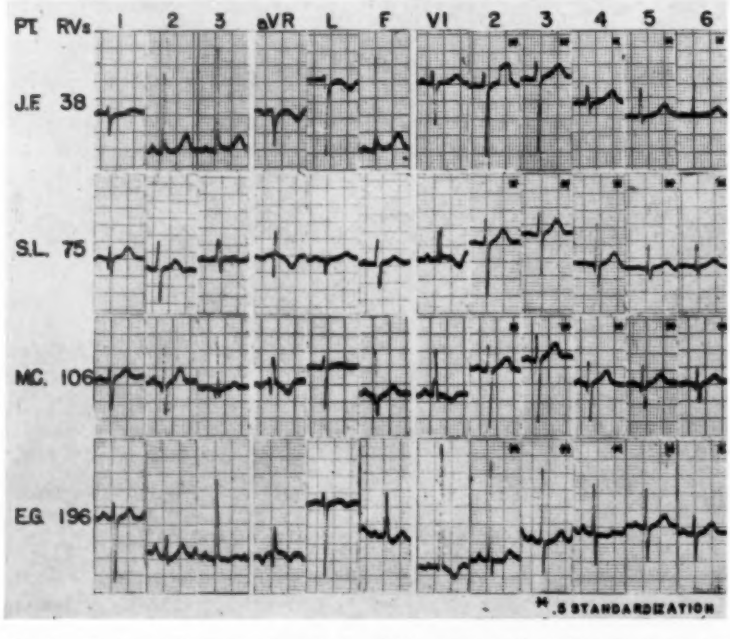


Fig. 4. Electrocardiograms of patients whose x-rays and cardiac pressures are shown in Fig. 2. Note increasing evidence of right ventricular hypertrophy as pressure rises.

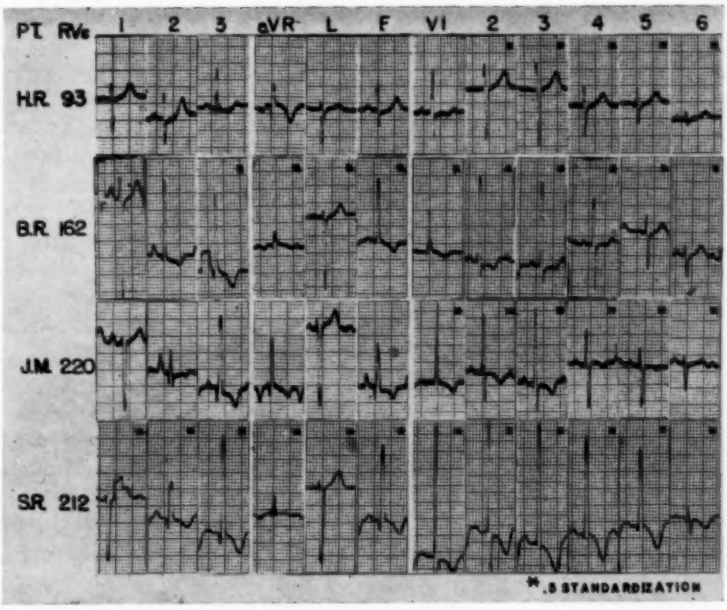


Fig. 5. Electrocardiograms of patients illustrated in Fig. 3. There is evidence of marked right ventricular hypertrophy and "strain" and of right auricular enlargement in the three patients with pressures over 140 mm. Hg.

there is a relationship between the level of right ventricular systolic pressure and the individual measurements.

As a single measurement, each feature was fallible, but when all features were considered together, it was found that increasing increments of right ventricular systolic pressure were associated with additional abnormalities unusual in patients with milder degrees of obstruction and that some features were found only in those with mild stenosis (see Figs. 1 and 4-6).

When the electrocardiogram was normal, as it was in 7 patients, the right ventricular pressure was below 50 mm. When the electrocardiogram showed only right axis deviation, a predominant R or R′ wave of less than 10 mm. in V_1 and in the right arm lead, or a pattern of rsr′ or rsR′ in V_1 or V_{3R}, the pressure was 80 mm. or less. Abnormalities of P waves, T waves, or S-T segments were not observed.

When the R wave in V_1 was more than 10 mm. in amplitude, the pressure was over 80 mm. Hg. When there was reversal of the normal R and S relationship across the precordium so that the S wave was the predominant deflection in V_5 or V_6, the pressure was 100 mm. or more.

When the right ventricular systolic pressure was over 140 mm., the R wave in V_1 exceeded 20 mm. in amplitude and new abnormalities appeared. These included high, peaked P waves, leftward displacement of the transitional zone, and deep inversion of the T waves in the right precordial leads, aV_F, and often in leads 2 and 3. The changes in the T waves were frequently associated with depression of the S-T segments in the same leads. Increasing elevations of right ventricular pressure above 140 mm. were marked by an exaggeration of these abnormalities. Half of these patients showed a qR configuration in the right precordial leads.

Some other features were found to be relatively insensitive in distinguishing the mild, moderate, and severe cases since they

Table I

Age in years	*Systolic pressure in right ventricle in mm. Hg*		
	<80	*80-140*	*>140*
<2	0	1	2
2-5	6	4	11
6-10	7	6	3
11-15	10	4	2
16-20	3	3	2
21-25	0	2	3
26-30	1	0	2
31-35	2	0	0
36>	1 (54 yr.)	2 (48, 51)	0
Total	30	22	25

Table II. Correlation coefficient between systolic pressure in right ventricle and:

Amplitude R V_1	0.88
Amplitude S V_6	0.77
Amplitude P 2	0.74
Leftward spread of precordial T wave inversion	0.63
Leftward displacement of precordial transitional zone	0.56

were almost always present in those with systolic pressures over 50 mm. Hg: these were right axis deviation, predominant R wave in lead aV_R, and delayed intrinsicoid deflection of the R wave in V_1.

Amplitudes of the R and S deflections in the limb leads were not tabulated separately since they bore a close resemblance to the amplitudes described in the right and left precordial leads (Figs. 1, 4, and 5). Patients with an abnormally tall R wave in V_1 and deep S in V_6 showed a tall R in aVF and lead III and a deep S in lead I.

In column 7 of Fig. 6 are listed the various patterns of "incomplete right bundle branch block": rsr′, rSr′, rsR′, rR′, and qR. They are combined as one group because they probably have the same significance: a conduction disturbance in the right ventricle. Furthermore, when the initial deflections are of small amplitude, it is sometimes difficult to differentiate qR from rsR′, and, in the same patient, both forms may be present in the same or different leads. With these reservations in mind, it was interesting to note that those with mild stenosis showed the rsr′ or rsR′ configuration (14 out of 30) but not a qR pattern; those in the middle range of pressures rarely showed a conduction disturbance; and those with pressures above 140 mm. Hg often showed a qR pattern (12 out of 25 patients) while only 3 displayed a rsR′. Thus from this figure it would appear that a pattern of "incomplete right bundle branch block" was not a discriminating feature, yet in actuality it was helpful, both as to form of the complex and amplitude of the late R wave.

Postoperative electrocardiograms taken at the time of recatheterization in 10 patients who had a residual systolic gradient between right ventricle and pulmonary artery were compared with those in patients with pulmonic stenosis who were not operated upon. When they were evaluated 3 to 5 years after transventricular valvulotomy, 3 young adults had systolic pressures that were lower than before operation but were still significantly elevated at 95, 110, and 189 mm. Hg. One of these was first catheterized 3 months postoperatively and later 3 years after the Brock procedure. The electrocardiogram and pressure measurements were similar on both occasions. Seven of the 10 postoperative studies were performed on children 10 to 24 months following transarterial pulmonary valvulotomy. Minimal systolic gradients of 5 to 15 mm. Hg were present in these 7; in none did the systolic pressure in the right ventricle exceed 35 mm. Hg. Serial electrocardiograms were obtained at frequent intervals postoperatively, and it was found that electrocardiographic changes indicative of regression of hypertrophy occurred chiefly during the first year after operation. The records at postoperative catheterization corresponded with those of unoperated patients at the same pressure level.

DISCUSSION

Periodic cardiac catheterizations to assess severity of pulmonic stenosis and to follow

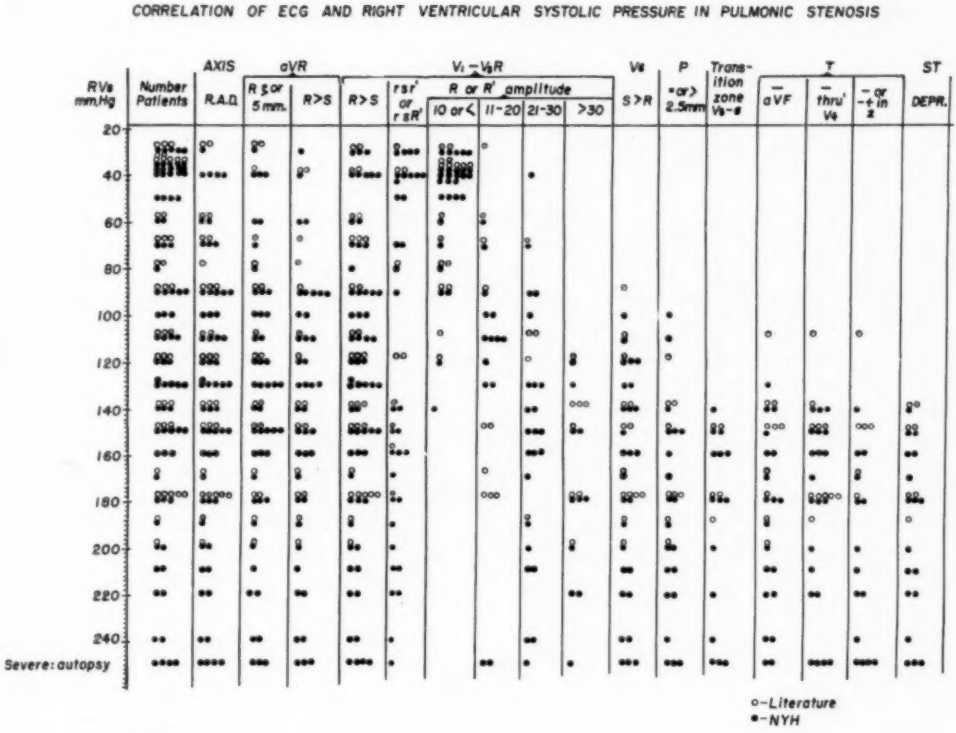


Fig. 6.

its progression or its regression after operation are impractical. But if a simple tool were available that corresponded well with direct pressure measurements, then some of the uncertainty in patient management could be eliminated. One would not withhold operation from an "asymptomatic" person with severe stenosis, nor would one needlessly restrict activities or suggest surgical treatment to a patient with a "stenotic" murmur and prominent pulmonary artery but with mild stenosis. Ideally, patients might then be selected for preoperative cardiac catheterization in anticipation of surgery when the electrocardiogram indicated moderate elevation of right ventricular pressure. The improvement achieved after operation might similarly be appreciated by the level to which the electrocardiographic evidence of right ventricular hypertrophy regressed. The results presented show that electrocardiographic analysis does fulfill the need for a simple guide to the burden on the right ventricle in this condition, both in the unoperated and in the postoperative patient.

The electrocardiographic patterns fall into 3 broad groups: pressure below 80 mm. Hg (mild stenosis), 80 to 140 mm. Hg (moderate stenosis), and over 140 mm. Hg (severe obstruction). This division has practical value from the surgical standpoint, because current recommendations concerning operation depend in general on these same groupings. Operation is usually not advised for those with a right ventricular pressure below 80 mm. Hg. Patients with pressures of 80 to 140 mm. Hg in the right ventricle might be considered the ideal candidates for operation since the burden on the right ventricle is sufficiently severe to warrant relief, and the risk of operation is slight. Al-

though there is little doubt that patients in the third group need help, the risk of operation is greater, particularly if the pressure is in excess of 200 mm. Hg or if there is cyanosis or heart failure.

This study corroborates and extends the observations of others on the electrocardiographic findings in "pure" pulmonic stenosis. A means of quantitating the electrocardiographic changes with severity of stenosis was offered in 1955 by Sodi-Pollares and Marsico.[13] Silverman and associates[14] in 1956 pointed out the statistically significant correlation between the amplitude of the R wave in V_1 and the level of systolic pressure in the right ventricle. This observation was confirmed by Kjellberg and associates,[15] by Keith, Vlad, and Rowe,[16] and by Hanson.[17] In 1958, Cayler, Ongley, and Nadas[18] extended Silverman's study of 20 patients to a larger group of 150 patients from the same institution and concluded that, although the pressure in the right ventricle could not be accurately predicted from the voltage of R in V_1, there was a definite quantitative correlation between the electrocardiogram and the systolic pressure in the right ventricle.

The present report stresses the importance of analysis of several features of the electrocardiogram, the most important of which are the amplitudes of R in V_{3R}-V_1 and of S in V_{5-6}, the location of the transitional zone in the precordial leads, the depth of T wave inversion and depression of ST segments in precordial leads over the right ventricle and the related limb leads (aV_F, II, and III), the reversal of the normal R and S relationship in the V leads, and increased amplitude and peaking of the P wave. Interpretation of severity of pulmonic stenosis from the electrocardiogram gains accuracy by analysis of multiple variables such as these.

Several factors influence the electrocardiographic expression of right ventricular burden, so it is not surprising to find that there is no single feature which is entirely reliable. For example, the height of the R wave in V_1 is the best single guide, yet it is only when there is clearly a predominant positive or negative deflection in the QRS complex that the amplitude of R is meaningful with regard to right ventricular pressure. Attention to the position of the transitional zone and often exploration of leads farther to the right are necessary before interpretation can be made. Furthermore, the height of the R wave is influenced by a conduction disturbance over the right ventricle and tends to be higher if there is a late R wave than if there is an early one.

For similar reasons, the depth of the S wave in V_{5-6} does not regularly increase as the right ventricular pressure rises. The measurement becomes a reliable guide if one can be sure that these leads are to the left of the transitional zone. When there was no q wave evident, measurement of the intrinsicoid deflection in the right and left precordial leads was helpful in determining this point. In patients with moderate and severe obstruction, the intrinsicoid deflection was consistently later to the right of the transitional zone than to the left. Leads still farther to the left (V_{7-8}) may need to be studied and in some patients are more representative of events over the left side of the heart than are V_{5-6}.

While leftward displacement of the transitional zone was common in those with moderate and severe obstruction, interpretation of the position of the transitional zone was sometimes difficult because it was displaced so far to the left or, exceptionally, so far to the right that it was hard to locate, and also because there were sometimes 2 areas of transition. In a few patients, an Rs configuration was present in V_{3R} and V_1, that changed to rS in V_{2-3}, RS in V_4 or V_5, and qRs in V_5 or V_6.

The leftward spread of T wave inversion might be expected to be more reliable in adults than in children, since T wave inversion may be normal through V_4 in the latter. It is of interest that this measurement was helpful in assessing severity of stenosis, even in the very young, because only one patient with a right ventricular pressure below 120 mm. Hg demonstrated

inversion of T waves through V_4. The single exception was a postoperative patient, aged 2 years at recatheterization, who had an incomplete right bundle branch block and a right ventricular pressure of 35 mm. Unusual depth of inverted T waves was as characteristic of right ventricular "strain" and marked hypertension as was the spread of T wave inversion across the precordium.

SUMMARY AND CONCLUSIONS

A study was made of electrocardiograms obtained close to the time of cardiac pressure measurement in patients with pulmonic stenosis without a left-to-right shunt and with intact ventricular septum. Seventy-three were from The New York Hospital and 41 from reports in the literature. While the amplitude of the R wave in V_1 gave the highest correlation with systolic pressure in the right ventricle, analysis of multiple features was found more accurate than a single one. The composite evaluation permitted distinguishing among patients with mild (R.V. systolic pressure below 80 mm. Hg), moderate (pressure 80 to 140 mm.), and severe stenosis (pressure over 140). Postoperatively, regression of the electrocardiographic abnormalities occurred chiefly during the first year after operation. The form of the tracings at that time correlated with the right ventricular pressure. The electrocardiogram was found to fulfill the need for a simple yet reliable tool to estimate the burden on the right ventricle in the presence of pulmonic stenosis with intact ventricular septum.

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A study of the I^{131} uptake in children, with special reference to the iodide repletion test

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RELATIVELY few reports are available on the uptake of radioactive iodine as a test of thyroid function in children. This is probably due to the potential hazards of irradiation of the neck in the pediatric age group. Oliner and others,[1] however, have pointed out that even with tracer doses as large as 25 μc the concentration of radioactive iodine in the gland of a child would be much below the maximal permissible I^{131} concentration of 4.15 μc per kilogram.[2] The ease by which the test is performed compared with the technical difficulties of protein-bound iodine, butanol extractable iodine or basal metabolic rate determinations, as well as its independence of the nervous state of the subject, renders it a useful preliminary test in various thyroid disorders in childhood.[3]

The uptake of radioactive iodine, however, measures the dynamic function of the thyroid gland and not its hormonal production or content.[4] The test thus measures the trapping ability of the gland which might be influenced by certain extrathyroid factors such as the dietary iodide, renal iodide clearance, and the thyroid blood flow.[5] Furthermore, the degree of purity of the radioiodine used and the technique both influence the results of the test. These variants might explain the differences in results reported by various workers.[1, 6-12] The uptake of radioactive iodine within a 24-hour period measured by these authors was in the range of 10 to 50 per cent. Most workers did not find marked differences between children and adults or between children of different ages.[1, 21] Van Middlesworth[13] reported 2 among 7 normal newborn infants with high uptakes of 46 and 97 per cent, respectively. Martmer[14] also reported relatively high uptakes in 16 premature infants (28 to 52 per cent). Differences in the 24-hour thyroid accumulation of I^{131} were also reported in different localities; thus the observed uptakes from persons on the east and west coasts of the United States[6-9] were lower than those from central United States.[1, 8] It was suggested that these differences are due to different contents of iodine in the diet.[1]

The aim of this study was to determine

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the normal uptake of radioactive iodine by the thyroid uptake of normal Egyptian infants and children of different ages during a 24-hour period. The I^{131} uptake by Egyptian children with various disorders of the thyroid will be the subject of another communication.

MATERIAL

One hundred nineteen normal Egyptian infants and children, aged 3 days to 12 years, were examined. These children were considered to be normal as far as the condition of the thyroid was concerned if their growth and development, including radiologic bone age, were within normal limits and if they were not suffering from any acute or chronic illness which might interfere with thyroid function at the time of the study. There was no family history of thyroid disease in any of the children examined. Protein-bound iodine[127] in 32 of these children was normal, ranging from 3.5 to 7.5 mg. per cent. Determinations of the basic metabolic rate were obtained in 22 of the older children; all were within the normal range. The children examined were all from Cairo, 200 kilometers from the seashore. They belonged to groups with moderate or low incomes. The daily diet of the children of the moderate income group included meat, beans, cereals, vegetables, and fruits; those of the low income group ate meat and fruits on the average only once a week. Fish and sea foods were only occasionally included in the diets. No fish or other seafood was eaten for 1 week before the test. None of the children received any drug which might interfere with the results of I^{131} uptake for at least 4 weeks preceding the test, such as iodine, thyroid, antithyroid drugs, para-aminosalicylic acid,[15] resorcinol,[16] and the like.

TECHNIQUE

The technique described by Werner and associates[17, 18] was used with some modifications. The tracer dose used was 5μc for infants and 10 μc for children. The dose was measured by means of a pipette and given in a paper cup with some water. The cup was refilled with water for the child to drink 2 or 3 times to ensure that the whole dose was received. For infants and younger children the tracer dose was administered by a gastric tube using a syringe; the dose was diluted with water. The syringe was refilled with water several times in the same way as the drinking cup.

A scintillation counter is used for counting 24 hours after the administration of the tracer dose. The counter is placed at a distance of 30 cm. from the neck. Three readings, lasting 100 seconds each, are taken. The mean count is calculated and corrected for the background irradiation from the room. This count gives the value of I^{131} in the thyroid, plus that of I^{131} in the neck outside the thyroid gland. A count is then made in a similar way at a distance of 30 cm. from the midthigh after evacuating the urinary bladder. The thyroid I^{131} uptake is obtained by subtracting the thigh count from the neck count. A standard is prepared by placing the same dose given to the subject in a 25 ml. volumetric flask. The bulb of the flask is filled with water, but not the neck. The flask is then submerged in a 1,000 ml. beaker filled with water, with a distance of 1 cm.

Table I. Results of 24-hour thyroid uptake in 119 Egyptian children

Age group (in years)	*Total no. of cases*	*Group I (cases with normal uptake)*		*Group II (cases with high uptake)*	
		No. of cases	*Range of uptake (%)*	*No. of cases*	*Range of uptake (%)*
1	17	12	20.0 to 48.4	5	56.0 to 82.0
1 to 2	10	7	20.1 to 49.0	3	58.1 to 79.0
2 to 5	29	19	20.0 to 50.0	10	56.3 to 98.0
5 to 10	43	25	18.9 to 51.6	18	61.0 to 78.8
10 to 12	20	9	18.7 to 52.1	11	59.2 to 95.0

kept between the flask and the side of the beaker in order to simulate the neck tissues around the thyroid. The count is obtained at a distance of 30 cm. from the scintillator, and the mean of 3 different readings is taken and corrected for the background irradiation. The percentage of thyroid I^{131} uptake is calculated from the formula: Percentage of

$$\text{uptake} = \frac{\text{neck count} - \text{thigh count}}{\text{standard count}} \times 100.$$

RESULTS

The results were classified into two groups. Group I included children who showed a normal 24-hour I^{131} thyroid uptake as compared with adults. Group II included children who showed an abnormally high I^{131} uptake. The make-up of the two groups was equivalent in regard to sex, weight, height, surface area, and social status.

Group I. This group included 72 euthyroid children or 60.5 per cent of the 119 children examined. The 24-hour I^{131} thyroid uptake by these children was within the normal range for euthyroid Egyptian adults which was from 18 to 55 per cent in our laboratory. There was no relation between the uptake of I^{131} and the age, sex, weight, or surface area of the children in this group. Four of the 12 infants examined were aged 2, 12, 19, and 25 days, respectively. Their uptakes were 25, 31, 20, and 42 per cent, respectively.

Group II. This group included 47 or 39.5 per cent of the 119 children examined. The I^{131} uptakes for these euthyroid children were high as compared with the average for the euthyroid Egyptian adult. The age distribution of these children is shown in Table I; it will be noted that there is a direct relationship between age and the percentage of children in Group II.

DISCUSSION

The results of this study reveal that a relatively high proportion of normal Egyptian children (39.5 per cent) have an abnormally high uptake of I^{131} without any evidence of thyroid disease. Since these children were not suffering from cardiac or renal disease and were not receiving any drugs for 4 weeks previously, such high uptakes would, in all probability, be due to depletion of body stores of iodine secondary to iodine deficiency in the diet.[3] Iodine deficiency increases the I^{131} thyroid uptake through excessive production of the thyroid-stimulating harmone[19] and perhaps, to a lesser extent, through direct stimulation of the thyroid gland as a result of the low iodine levels.[20]

In 1957 Burnell and Fraser[21] standardized the iodide repletion test in order to detect such euthyroid cases with avid uptake due to depletion of body stores of iodine. The principle of the test is to administer enough

Table II. Iodide repletion test in children

Case no.	*Age*	*First uptake (%)*	*Iodide repletion test*		*Second uptake (%)*
			Dose of potassium iodide mg./day	*Rest period (days)*	
79	8	66.1	10	65	22.0
80	7	64.1	10	60	45.8
81	10	83.9	10	62	42.9
82	13	83.6	10	90	48.8
84	10	81.4	10	61	54.0
93	6	64.0	10	60	47.0
96	11	68.8	10	75	57.0
97	12	75.1	10	92	56.0
98	11	71.0	10	68	54.0
159	11	95.0	10	65	52.0
164	4	80.0	10	60	50.0
170	11	82.0	10	75	46.0
172	8	75.0	10	75	32.0
173	4	72.0	10	82	47.0
174	7	74.0	10	75	40.0
183	1	75.0	5	68	40.0
189	2	65.0	5	60	38.0
193	12	60.0	10	90	35.0
194	11	83.0	10	60	53.0
199	1½	70.0	5	65	51.0
202	8	72.0	10	60	48.2
206	6	69.2	10	60	50.1
209	12	89.0	10	60	56.0
210	10	78.8	10	60	50.8
228	9	73.4	10	62	46.2
Controls					
161	12	55.0	10	65	50.0
171	10	55.0	10	72	45.0
201	4	43.0	10	60	39.0
215	11	53.0	10	75	46.5
217	8	35.0	10	65	32.0
218	1½	32.0	5	60	27.5

iodine to correct any possible deficiency of body stores. The I^{131} uptake of the thyroid gland is then retested after a lapse of time in order to allow the body to excrete any excess iodine administered. Excess iodine might give falsely low results. After various preliminary experimentations, Burnell and Fraser standardized the test for adults as follows:

After the preliminary I^{131} uptake test, iodine was administered in the form of potassium iodide, 10 mg. daily for 14 days. This resulted in full restoration of the body stores of iodine in all instances.

The test with I^{131} was repeated at least 4 weeks later. Tests within shorter periods of time usually gave falsely low results because of the depressing action of excessive iodine on thyroid function. However, periods longer than 4 weeks gave equally good results.

We have utilized Burnell and Fraser's iodide repletion test with slight modifications to retest the euthyroid children with high uptakes in Group II. After preliminary studies, we have standardized the original iodide repletion test for children as follows: after the initial I^{131} thyroid uptake determination, potassium iodide in the form of a 1 per cent solution is given for 2 weeks in a dose of 5 mg. daily for infants (0 to 2 years) and 10 mg. daily for older children. The I^{131} uptake is repeated 2 months later; a shorter period occasionally gave abnormally low uptakes.

The iodide repletion test, thus modified, was carried out on 25 children belonging to Group II. The test was also carried out on 6 children of Group I, who served as controls. The results are shown in Table II and are diagramatically represented in Fig. 1.

It is evident from Table II that the iodine uptake for the 25 children of Group II approximated the normal range after restoration of the body stores of iodine. The uptake for the 6 control children decreased only very slightly, indicating that practically no excess of iodine was circulating after the rest period of 2 months. These data indicate that the abnormally high uptakes of I^{131} by euthyroid children in Group II are due to a

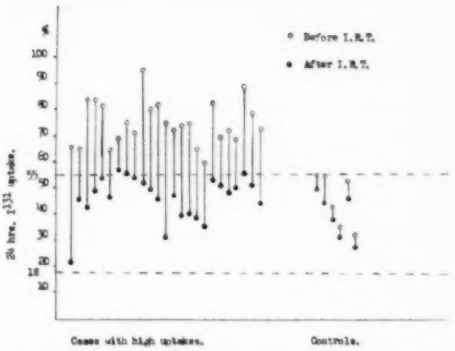

Fig. 1. Iodide repletion tests in children with previously high and normal uptakes of I^{131}.

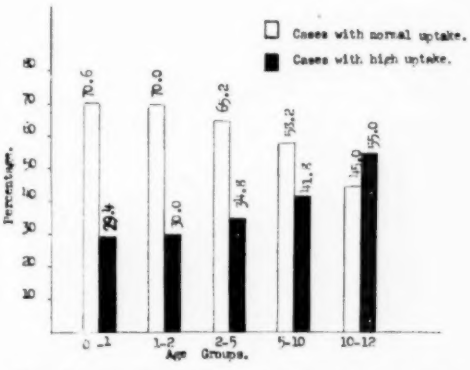

Fig. 2. Age distribution of Egyptian euthyroid children with normal and high I^{131} uptakes.

state of subclinical iodine deficiency, which apparently exists in a good percentage of normal euthyroid Egyptian children (39.5 per cent). It was demonstrated by animal experiments that iodine deficiency resulted in a marked increase of I^{131} uptake long before a goiter develops.[22]

It is interesting to analyze the age distribution of these euthyroid children with avid thyroid uptake. Fig. 2 shows diagrammatically the proportion of euthyroid children with normal and high uptakes in each age group.

It is evident from Fig. 2 that the percentage of euthyroid children with high uptakes increases with age. This is probably due

to the greater demand for thyroid hormone by the older child, thus accentuating the degree of iodine depletion.

SUMMARY AND CONCLUSIONS

I^{131} uptake was measured in periods of 24 hours in 119 euthyroid Egyptian children of different ages; 39.5 per cent of these children (47 children) showed abnormally high uptakes. A modified iodide repletion test was done on 25 of these children. The results indicated that a state of iodine deficiency is prevalent in apparently healthy Egyptian euthyroid children. Iodine deficiency was not related to sex, weight, surface area, or social status, but it seems to be more pronounced in older children. High uptakes of I^{131} must be interpreted with caution, and an iodide repletion test must be done before definite conclusions are made.

Introduction of iodine in the diet through iodination of table salt would seem to be a necessity in Egypt.

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Overwhelming infection in children following splenectomy

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THE OCCURRENCE of overwhelming infection in infants and children following splenectomy has been well documented. King and Shumacker[1] reported upon 5 infants who had severe infections subsequent to splenectomy. Three of these infants died as a result of these infections. In addition, Hoefnagel[2] and others[3-11] have recorded instances of postsplenectomy infectious disasters in infants and children. However, other authors[12-13] doubt that serious infection may be a significant consequence of splenectomy in infants and children.

Because the underlying disease necessitating splenectomy has often seriously compromised resistance to infection, it has been impossible to assess the clinical importance of these reports. The incidence of infection following splenectomy in such conditions as Aldrich's syndrome, reticuloendotheliosis, neutropenia and aplastic anemia must be evaluated against the known high incidence of infection occurring prior to splenectomy. Similarly, leukemia, other malignant diseases, Cooley's anemia, agammaglobulinemia, chronic hepatic disease, collagen disease, and renal and heart disease may also lower resistance to infections. The exclusion of these conditions would allow a closer estimate of the effect of splenectomy on resistance to bacterial and viral infections.

Therefore, in assessment of the effect of splenectomy on increased susceptibility to infection, only patients who undergo splenectomy for such entities as familial spherocytic hemolytic anemia, idiopathic thrombocytopenic purpura, and traumatic rupture of spleen should be considered. In the natural history of these processes there is no increased incidence of infection prior to splenectomy. A follow-up study of infants and children who had splenectomy for these diseases would provide meaningful data.

The purpose of this report is to analyze the records of those children aged 16 or less who had splenectomy performed from 1942 through July, 1957. The review was accomplished by obtaining follow-up data on patients who had splenectomy done at the University of Minnesota Hospitals, Ancker Hospital, and Children's Hospital in St. Paul and at the Minneapolis General Hospital.

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Part of this work was done during the tenure of a Postdoctoral Research Fellowship, National Heart Institute, United States Public Health Service. Address, Department of Pediatrics, The Medical School, University of Minnesota, Minneapolis 14, Minn.

The survey revealed 78 patients who had undergone splenectomy for spherocytic hemolytic anemia, idiopathic thrombocytopenic purpura, or traumatic rupture of the spleen. Patients with conditions known to predispose to infection were excluded. Current follow-up was obtained in 74. The shortest duration of follow-up was 2½ years.

METHODS

The diagnosis of each of the conditions for which follow-up was obtained was made by the following criteria:

A. Spherocytic (familial) hemolytic anemia was diagnosed by the presence of spherocytes in peripheral blood of the patient and other family members. Acquired hemolytic anemia was eliminated by a negative Coombs test where other members of the family did not have spherocytes in peripheral blood.

B. Idiopathic thrombocytopenic purpura was diagnosed when platelet count was below 80,000 per cubic millimeter and there were no other preceding or concomitant specific illnesses. The association of giant hemangioma and thrombocytopenia was classified as idiopathic thrombocytopenic purpura.

C. Traumatic rupture of the spleen was included only when the spleen was considered to be normal by examination of microscopic sections.

Choice of hospitals was made for following reasons:

A. Both Minneapolis General Hospital in Minneapolis and Ancker Hospital in St. Paul are the emergency treatment centers for their respective cities and counties. Inclusion of these two hospitals would increase the number of patients who had splenectomy for traumatic rupture of spleen.

B. Children's Hospital at St. Paul and University of Minnesota Hospitals at Minneapolis were chosen because as referral centers the admissions of children with idiopathic thrombocytopenic purpura and familial spherocytic hemolytic anemia are relatively high.

Two patients (Cases 1 and 2) were personally known to the authors to have had overwhelming infection prior to beginning the review for this report. They represent the stimulus for searching the literature and for reviewing the charts. As such, they are retained in the series.

If there were no recent hospital, clinic, or physician reports in the chart, a questionnaire was sent to the family physician. If follow-up could not be completed in this manner, a letter was sent to the parents.

RESULTS

The patients are reported in 3 groups, those having spherocytic hemolytic anemia, idiopathic thrombocytopenic purpura, or traumatic rupture of the spleen. Table I gives the distribution of patients by age and indication for splenectomy.

Spherocytic hemolytic anemia. Twenty-six patients had splenectomy. Two patients had subsequent infection and died. These cases are reported in detail in the summaries. Both of these patients were males, 6 and 7 years of age, and splenectomy was performed at the University of Minnesota Hospitals. One had well documented evidence of pneumococcal sepsis (M. H. No. 1) and the other had circumstantial evidence of overwhelming infection (S. S. No. 2).

Thrombocytopenic purpura. Thirty patients were reviewed. One patient in this group had subsequent infection and died. This case is reported in detail in the summaries. He was an infant with thrombocytopenia and giant hemangioma who had splenectomy at 3 months of age and who died at 7 months of age from a sudden overwhelming infection (T. G. No. 3).

Traumatic rupture of the spleen. There were 18 patients. No infections were noted in this group.

The diagnosis in the 4 cases which were lost to follow-up was as follows: spherocytic hemolytic anemia 2, thrombocytopenic purpura 2.

Antibiotics were used prophylactically following splenectomy in only one of the 74 patients available for follow-up.

Table I. Distribution of patients undergoing splenectomy by age and indication for splenectomy

	Age (years)			
	Under 1	*1-5*	*6-10*	*11-16*
Spherocytic hemolytic anemia	4	7	10*	5
Idiopathic thrombocytopenic purpura	2†	9	8	11
Trauma	0	4	6	8

*Two deaths.

†One death.

DISCUSSION

The spleen, one of the integral parts of the reticuloendothelial system, is able to clear bacteria from blood.[15, 16, 17] The spleen is more effective per unit of weight than is the liver; the liver, however, is more important by virtue of its larger size.[18, 19] Encapsulated organisms are removed less efficiently by the reticuloendothelial system than are nonencapsulated bacteria.[20] This is of interest in view of the preponderance of encapsulated organisms, particularly *Diplococcus pneumoniae,* reported in the cases of fulminating infection in splenectomized children.[3, 5, 7, 11]

The precise role of the spleen in antibody production is controversial. Response of splenectomized animals and humans to antigenic stimulation has not been uniform. The variables of experimental pathology which dictate choice of animal and the method of antigenic stimulation profoundly influence results obtained. The interval at which antibody responses were measured and the previous exposure to antigen are other factors complicating interpretation.[21, 22, 23] The interval of time between splenectomy and antigenic stimulation introduces a further variable.

These factors are apparent in the excellent study done by Taliaferro.[19] Using rabbits as subjects and sheep erythrocytes as antigen, the hemolysin titers produced by intact and splenectomized rabbits were compared. The differences, which were assumed to be antibody originating from the spleen, were statistically significant. "Splenic antibody" appeared sooner, reached a higher level, and disappeared sooner than "nonsplenic antibody." Saslow and associates[24] have recently studied the immunologic capacity of splenectomized patients. They found that 90 per cent of these adults and older children were able to produce antibodies in amounts equal to that produced by controls. A small number of splenectomized patients, however, showed a lesser antibody response than controls.

These findings suggest that the spleen may be more effective in synthesizing antibody than the nonsplenic sources in the first few days following antigen stimulation and that in man a change in immunologic capacity after splenectomy may be an individual characteristic rather than a regular consequence. This hypothesis might provide an explanation for the infrequent clinical association of overwhelming infection and splenectomy. A study done by Laski and MacMillan[13] compared follow-up in 81 children undergoing splenectomy and 94 children after appendectomy. One child in each group had purulent meningitis. This suggests the incidence of serious infection in the remote postoperative period in the patient after splenectomy is comparable to the incidence after appendectomy. Whether these findings are fortuitous, related to surgical trauma or to loss of the small amount of lymphoid tissue found in the appendix, cannot be ascertained at present.

As noted, one essential to an evaluation of the effect of splenectomy on resistance is the elimination of other conditions that predispose to infection. Most of these are obvious. Some, however, may be unrecognized. A syndrome described by Aldrich[14] is an example of one such entity. These patients have eczema, thrombocytopenic purpura, and marked susceptibility to infection. Their inclusion in prior series doubtless has contributed to the impression that splenectomy has a deleterious effect.

Assuming no other unrecognized factors are operative, it appears from our data that there is only a slight, but real, increased

susceptibility to infection in patients who have undergone splenectomy. The value of data obtained in our review and in other reports lies in its application to decisions regarding indications for splenectomy. Though not borne out in our cases, the apparent greater vulnerability of young infants to infection would make one more conservative in the treatment of patients in the first year of life. In the older child the established indications for splenectomy are not vetoed by the slight risk of overwhelming infection. It would appear prudent to follow the child who has had a splenectomy carefully and to treat all infections vigorously at their onset.

SUMMARY

1. A follow-up review of patients who had splenectomy for spherocytic hemolytic anemia, thrombocytopenic purpura, and traumatic rupture of the spleen was accomplished.

2. A total of 74 patients were obtained by chart review.

3. Three patients had fatal infections subsequent to splenectomy, which was performed in 2 cases for spherocytic hemolytic anemia, and in 1 for thrombocytopenic purpura.

4. No patients in our series who had splenectomy for traumatic rupture of the spleen had subsequent infection.

CASE SUMMARIES

Case 1 (M. H. No. 906302). This 6½-year-old boy had been in good health until Nov. 20, 1956, when he developed tonsillitis and cervical adenitis. During the care of this illness a palpable spleen was noted and a peripheral blood smear revealed spherocytes. The family history was negative for anemia and/or jaundice.

Physical examination revealed him to be pale, well developed, and well nourished. He had acute pharyngitis and tender anterior cervical adenitis. The spleen was palpable 2 cm. below the left costal margin and was firm and nontender.

Laboratory examination included hemoglobin 13.0 Gm., serum bilirubin 0.2 mg. direct and 1.4 mg. total, reticulocyte count 8.6 per cent, and fecal urobilinogen 121 mg. per day. The saline red cell osmotic fragility was increased with beginning hemolysis at 0.72 per cent saline and complete hemolysis at 0.36 per cent saline. The mean corpuscular diameter was 6.1 μ. The patient's red blood cells had a Cr^{51} half life of 15 days when transfused into a normal patient. The Coombs test was negative.

The patient's infection responded to penicillin therapy and on Jan. 2, 1957, the spleen was removed. The surgery and postoperative course were uneventful.

The boy appeared completely well until 3 A.M., May 16, 1957. At that time he developed headache and emesis. Shortly thereafter he became lethargic and incoherent and was brought to the University of Minnesota Hospital at 6 A.M. Examination revealed an acutely ill, comatose child. Temperature was 105° F., pulse 180, and blood pressure 50/0. Injection of both tympanic membranes was present and the neck was slightly stiff. The remainder of the examination was normal. A lumbar puncture was normal.

A blood culture was drawn and the patient received penicillin, sulfadiazine, and streptomycin. He was given hydrocortisone 100 mg. intravenously and a blood transfusion was started. His condition continued to deteriorate and, despite tracheotomy and cardiac massage, the patient died at 9:50 A.M. The blood culture revealed a *D. pneumoniae* on pour plate with 1,000 colonies per cubic centimeter.

Postmortem examination. Abnormal findings at postmortem were limited to the lungs. The lungs were mottled, solid to feel, and had purple discoloration. Microscopy revealed marked diffuse atelectasis, alveolar hemorrhage, and numerous acute inflammatory cells in the alveoli and bronchioles. Postmortem blood cultures were negative.

Summary. This 6½-year-old boy had a splenectomy for spherocytic hemolytic anemia. He died suddenly of pneumococcal pneumonia and sepsis after a symptom-free interval of 5 months.

Case 2 (S. S. No. 891160). A 7-year-old boy had onset of weakness, malaise, anorexia, and jaundice in May, 1955. The patient's three siblings and father had clinical and laboratory evidence of familial hemolytic anemia. In November, 1955, he was admitted to the University of Minnesota Hospital. Physical examination revealed the spleen palpable at the left costal margin. Peripheral smear revealed spherocytosis and a mean corpuscular diameter of 5.7 μ. Osmotic saline red cell fragility test showed beginning hemolysis at 0.66 per cent saline and completion at 0.36 per cent saline. Fecal urobilinogen was 219 mg. per day. Bone marrow biopsy revealed erythroid hyperplasia. The Coombs test was negative. The reticulocyte count was 5.8 per cent and the hemoglobin was 11.1 Gm. per cent.

Splenectomy was accomplished on Dec. 14, 1955, with no complications.

The patient returned home and was asymptomatic. Examination in clinic on Jan. 13, 1956, July 13, 1956, and Oct. 11, 1956, revealed a healthy boy. His only illness during this period was an upper respiratory infection that resolved without therapy.

He continued to be well until March 2, 1957. On this date he ate a hearty noon meal. At 2 P.M. he vomited and had a temperature of 103° F. He continued to have a fever the remainder of the day. His physician saw him at 1:30 A.M. on March 3. Examination revealed a moderately ill, alert boy. Temperature was 104° F. He had a mild pharyngitis and a few râles at the lung bases. His neck was supple. The patient received an injection of penicillin and tetracycline was prescribed orally.

At 2:30 A.M. his condition suddenly worsened and he was dead on arrival at the local hospital shortly thereafter.

Postmortem examination. The body was that of a well-developed, 7-year-old boy with blotchy, cyanotic skin. There were no pleural adhesions. The bronchial mucosa was deeply injected and a moderate amount of foamy reddish-brown material was contained in the bronchi. The sectioned surfaces of the lung were moist and pink and the lower lobes were heavier than the upper lobes.

The adrenal glands were of normal size. There were splotchy areas of hemorrhage on the surface of each gland.

There was no other evidence of hemorrhage, and the heart, liver, gastrointestinal system, genitourinary system, and brain were normal. The spinal fluid was clear.

Microscopic examination revealed evidence of early bilateral bronchopneumonia. The adrenals showed areas of focal hemorrhage, more prominent in the medullary portions. A lymph node revealed acute adenitis. The remainder of the tissues were not remarkable.

Summary. This 7-year-old boy had a splenectomy for spherocytic hemolytic anemia in December, 1955. After an asymptomatic interval, he died suddenly on March 3, 1957, apparently with an acute overwhelming infection and Waterhouse-Friderichsen type syndrome.

Case 3 (*T. G. No. 812189). This boy had a normal neonatal period. At age 6 weeks a small soft purple subcutaneous mass was noted at the angle of the right mandible. This mass became progressively larger and he was admitted to the University of Minnesota Hospital for evaluation on Nov. 15, 1949, at the age of 8 weeks. The patient was otherwise asymptomatic.

Physical examination revealed a 7 by 7 cm. subcutaneous mass involving the right angle of the jaw, the right cheek, right pinna, and right anterior neck. It was soft, nontender, slightly movable, and the overlying skin was ecchymotic. The remainder of the examination was normal.

Shortly after admission the mass became suddenly larger. Hemorrhage into the mass was suspected and a platelet count at that time was 22,000. Further laboratory work included hemoglobin 8.9 Gm. per cent, white blood count 8,000 per cubic millimeter with a normal differential; bleeding time 6 minutes, normal prothrombin time. Four repeat platelet counts ranged from

*Previously reported by Good, Carnazzo, and Good.[33]

24,000 to 48,000 per cubic millimeter. Bone marrow examination revealed mild erythroid hyperplasia, megakaryocytosis, and minimal platelet formation.

A diagnosis of hemangioendothelioma with thrombocytopenic purpura was made. Surgical removal of the mass was deemed desirable and on Dec. 2, 1949, a splenectomy was done in an attempt to alleviate the thrombocytopenia. The postoperative course was uneventful but no improvement in the thrombocytopenia resulted. The patient was hospitalized for 8 weeks following operation and the platelet count ranged from 24,000 to 70,000 per cubic millimeter.

Examination 5 months postoperatively revealed normal growth and development, the mass unchanged, and a platelet count of 24,000.

This child continued to be free of symptoms until 1 A.M. on May 9, 1950, when high fever, vomiting, and instability began. The patient was seen by his physician at 9 A.M. and a temperature of 105° F., dyspnea, basilar râles, and slight cyanosis were present. He was placed on chloramphenicol by mouth. His condition became worse and when seen again at 6 P.M. the patient appeared moribund. He died shortly thereafter en route to the University of Minnesota Hospital. This patient had had no prior infection, no eczema, and no evidence of hemorrhage during his acute terminal illness. He was not treated with steroid hormones at any time during his illness.

Postmortem examination. Pertinent findings were restricted to the lungs, adrenal glands, and the tumor mass.

The lungs were heavy and indurated. Pink, patchy fluid exuded from the cut surfaces. Microscopic examination revealed extensive atelectasis and edema of the alveoli. No inflammatory cells were present.

The left adrenal gland was grossly hemorrhagic. There was extensive extravasation of erythrocytes throughout the cortex on microscopic examination. The right adrenal was normal.

The hemangioma measured 6 by 3.5 by 3.5 cm. It was well encapsulated, dark, firm, cellular, and hemorrhagic. Microscopic diagnosis was benign hemangioendothelioma.

There was no evidence of hemorrhage in the brain or other viscera of this patient. Postmortem blood cultures were not obtained.

Summary. This patient underwent splenectomy at the age of 10 weeks for thrombocytopenia. He died suddenly presumably of overwhelming infection and adrenal hemorrhage after a symptom-free interval of 5 months.

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The effects of intermittent doses of adrenocortical steroids on the statural growth of nephrotic children

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LINEAR growth of children with nephrosis is retarded during the active phase of the disorder and becomes accelerated during spontaneous or induced remission.[1] Since adrenocortical steroid therapy is widely employed to maintain remission in nephrosis[2-4] it is of interest to ascertain whether the known growth-suppressing influence of corticosteroids[5, 6] modifies the accelerated growth pattern observed during the remission of untreated nephrosis.[1]

To assess these factors we have examined the growth patterns of 2 groups of children with nephrosis. One group received intermittent steroid therapy to maintain remission and the other group did not.

MATERIALS AND METHODS

Data were collected from 35 children with the nephrotic syndrome. The diagnosis in each case was established by the usual criteria of albuminuria, hypoalbuminemia, and hypercholesterolemia. The children were divided into two groups as follows.

Group A. This control group consisted of 18 patients with nephrosis who were observed following the elimination of edema fluid. In 4 of these patients diuresis had occurred spontaneously. Of the remaining 14 patients in whom remission was induced by corticosteroids,* 6 received the drug for 10 days and 8 received the medication for 28 days. This group consisted of patients treated during our early trials of steroid therapy, before we adopted intermittent maintenance steroid therapy as a regimen in the management of children with nephrosis. Hence they were not treated contemporaneously with the patients in Group B (vide infra) and have been under observation for a longer period of time.

Group B. This group consisted of 17 patients who received cortisone and/or prednisone on an intermittent basis for peri-

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*Cortisone and the adrenocortical-active analogs will henceforth be referred to as steroids.

ods varying from 7 to 22 months following the elimination of the edema fluid. Steroids were administered for 3 to 4 consecutive days of each week in doses ranging from 60 to 500 mg. of cortisone per square meter of surface area per day.*

When indicated, supplemental potassium was given, and all patients received single daily oral doses of an antibiotic (Bicillin 300,000 units)† for varying lengths of time.

The two groups of patients were comparable in composition as judged by the criteria of age, sex distribution, initially observed height, known duration of illness before our first observation, and total duration of proteinuria. No statistically significant differences are demonstrable in these parameters as listed in Tables I, II, III, and IV.

Neither progressive renal disease nor evidence of impairment in renal function was evident in any patient in either group during the course of this study. By our criteria[4] both groups consisted of patients with disease of comparable benignity.

Values for height are those ordinarily obtained at a patient's periodic visit to the clinic. We believe that any variability arising from individual differences in techniques of measuring is to a large degree cancelled out by the numerous serial values that were available for each child in each group. The people who obtained and recorded the values for height had no knowledge of any division of the patient population into groups.

RESULTS

Tables I and II show the physical characteristics of the control group (A) and the maintenance-steroid group (B), respectively.

Tables III and IV show the values for height recorded at 5 selected points over the period of observation in the patients in Groups A and B, respectively. The time intervals between the points of observation are given at the right of Tables III and IV. The points selected were as follows:

1. The time at which the child with nephrosis was first observed in our clinics.

2. The time at which remission of the disease was considered to have occurred (e.g., not more than a trace of albumin in random urine specimens with a specific gravity of 1.018 or higher).

3. The time at which intermittent maintenance steroid therapy was discontinued in patients in Group B. The time period between points 2 and 3 averaged 8 months in Group B. In Group A, point 3 was established to obtain a time interval comparable with Group B. Hence, in Group A, point 3 also averaged 8 months after point 2.

4. The time of our last observation of the patients in Group B, averaging 11 months after point 3. Again, this point was established in Group A patients to approximate the same time interval and averaged 11 months after point 3.

Table I. Data of patients in Group A (control group)

Patient	*Sex*	*Age* (months)*	*Duration of proteinuria (months)*
1. K. D.	F	106	7
2. E. S.	F	73	8
3. P. F.	F	148	36
4. S. S.	F	48	17
5. R. M.	M	59	28
6. M. C.	M	128	21
7. J. G.	M	57	36
8. B. W.	F	26	7
9. C. P.	F	42	18
10. M. Y.	F	39	13
11. J. B.	M	36	10
12. S. R.	M	37	17
13. S. C.	M	23	6
14. M. M.	M	74	3
15. M. D.	F	66	20
16. M. H.	F	66	8
17. V. W.	F	27	14
18. M. D.	F	64	9
	Mean	62.2	15.4

*When proteinuria ceased.

*Prednisone was assumed to possess 5 times the activity of cortisone by weight in order to calculate comparable doses.[7]

†Supplied by the courtesy of Wyeth Laboratories, Philadelphia, Pa.

Table II. Data of patients in Group B (those receiving therapy)

Patient	*Sex*	*Age* (months)*	*Cortisone dosage†*		*Length of intermittent therapy (months)*	*Duration of proteinuria (months)*
			(mg./M.²/ day)	*Type of steroid‡*		
1. A. P.	F	39	150	P	10	4
2. R. G.	M	66	190	P	20	33
3. N. M.	M	82	135	P	7	24
4. J. P.	M	52	120	C+P	20	30
5. K. W.	M	77	120	P	11	16
6. M. A.	F	48	115	P	16	11
7. R. C.	M	51	80	C	10	15
8. W. S.	M	36	145	C+P	22	11
9. L. Z.	F	36	120	P	8	10
10. J. B.	F	79	130	C+P	9	5
11. D. M.	F	37	140	P	11	8
12. R. R.	F	77	100	P	7	10
13. W. P.	M	73	115	P	10	2
14. W. S.	M	64	500	C	9	3
15. J. M.	M	105	350	C	10	34
16. R. T.	M	37	380	C+P	12	23
17. P. G.	M	60	500	C	11	7
	Mean	60	199		12	14.5

*When proteinuria ceased.

†When prednisone was administered the amount listed is 5 times the actual dose. This was done to obtain equivalent cortisone dosages.[7]

‡C = cortisone; P = prednisone.

Table III. Heights of Group A patients during period of observation

Patient	*Heights (inches)*					*Interval between points of study* (months)*			
	*Points of study**								
	1	*2*	*3*	*4*	*5*	*1 to 2*	*2 to 3*	*3 to 4*	*4 to 5*
K. D.	46.00	49.25	50.50	53.00	54.75	6	7	11	11
E. S.	42.00	44.75†	46.75	51.50	53.00	7	8	14	23
P. F.	48.00	59.00	60.00			47	6		
S. S.	37.25	38.25	43.00	45.00†	50.00	5	13	10	23
R. M.	35.50	39.50	42.25	46.00	54.50	14	9	16	42
M. C.	51.00	55.25	56.50†	58.50		17	8	11	
J. G.	37.50	46.50	48.75	50.50	55.75	30	8	9	26
B. W.	35.00	36.00	37.25	41.00	53.00	3	7	12	48
C. P.	34.50	39.00	41.50	43.50	47.25	17	8	9	24
M. Y.	36.50	39.00	42.00	44.75	49.75	6	9	15	23
J. B.	37.00	39.00	40.75	44.00†	48.50	7	7	10	19
S. R.	37.00	37.75	40.50	42.50	45.25	6	8	10	15
S. C.	33.00	34.25	37.00	39.50		4	9	13	
M. M.	43.00	43.25	44.75	47.50		3	8	14	
M. D.	40.75	46.75				20			
M. H.	47.00	48.00	50.00	52.00		4	10	7	
V. W.	31.75	33.75	35.50	38.00	40.25	4	6	9	10
M. D.	39.50	41.50	43.50			8	5		
					Mean	11.6	8	11.3	22.9

*Point 1, when first observed; Point 2, when significant proteinuria ceased; Points 3 and 4, see text for explanation; and Point 5, when last observed.

†Interpolated value.

Table IV. Heights of Group B patients during period of observation

Patient	Heights (inches) Points of study* 1	2	3	4	Interval between points of study* (months) 1 to 2	2 to 3	3 to 4
A. P.	35.25	35.50	38.00	41.00	1	7	9
R. G.	37.00	45.50	47.75		32	8	
N. M.	46.25	53.25	53.75	54.50	27	6	3
J. P.	37.25	43.50	44.50	45.00	22	10	6
K. W.	42.50	46.00	49.50	52.50	19	14	17
M. A.	34.25	39.75	41.25	43.00	20	10	5
R. C.	38.00	42.50	43.50		13	3	
W. S.	29.75	34.00	36.25	39.75	15	9	15
L. Z.	35.75	36.50	39.00	42.50	4	10	12
J. B.	44.50	45.00	46.00	48.75	4	5	13
D. M.	33.00	34.50	35.50	37.00	7	8	5
R. R.	43.00	43.50	44.50	48.50	1	6	14
W. P.		46.50	49.50	52.25		10	12
W. S.		43.00	44.75	48.75		8	19
J. M.	51.00	51.50	53.75	56.00	3	11	15
R. T.	33.50	35.50	37.25	38.25	8	7	4
P. G.	40.00	40.75	42.75	45.50	3	7	14
			Mean		12	8.2	10.9

*Point 1, when first observed; Point 2, when significant proteinuria ceased; Point 3, when intermittent steroid therapy was discontinued; and Point 4, when last observed.

5. The time of our last observation of the patients in Group A: a reference point in time necessitated by the fact that Group A patients have been followed for longer periods of time than patients in Group B.

Table V and Fig. 1 summarize the growth increments in each group. Statistical significance was assessed by the use of Student's t test for the determination of probability (p) values.

The values for growth increments of patients in Group B during the period in which they received intermittent steroid therapy are significantly lower than of those in Group A during a comparable period of time.

DISCUSSION

All patients in the maintenance-steroid group received doses of a steroid exceeding 40 mg. per square meter of surface area per day, which Blodgett and colleagues[5] claim to be the growth-suppressive level of daily cortisone therapy.

No statistically significant differences in growth increment could be demonstrated between a small number of children in Group B who received cortisone intermittently and an equally small number in the same group who received prednisone intermittently.

The mean growth increment of each group is quite similar between points 3 and 4. This interval of time afforded the first opportunity of assessing the influence of the disease upon growth, apart from any steroid effect. The similarity in growth increments during this interval of time is taken as additional supportive evidence that the two groups form a reliable basis for comparison and that any differences in growth increments prior to this time may be of real significance in relation to the effects of steroids.

Growth increments within the *same* group were compared. The only statistically significant change occurred when intervals 3 to 4 and 4 to 5 were compared in the control group ($p = <0.05$). Growth increments were lower during the 4 to 5 than the 3 to 4 period. This could indicate a

slowing down of growth when, after a sufficient growth spurt during recovery from disease, these children approached their individually expected height.

Much of the above data agrees with the observations of Bauer[1] who studied the growth rates of 34 children with nephrosis. He concluded that, once evidence of the disease ceased to exist, a time interval approximating twice the length of their illness was required for these patients to attain their expected place on standard growth charts. He observed that patients who were the smallest for their age when first seen were those that eventually died. As he points out, this raises the question whether the disease was present for some time in a subclinical phase before it produced recognizable symptoms. The fact that detection of altered growth reflects changes occurring months previously lends some credence to his hypothesis. The possible error in relating low height:age ratios when first observed with a poor prognosis is apparent. Many genetically small children will be classed as having severe disease without real cause. The fact that several of our patients with severe disease leading to a fatal outcome did not have exceptionally low height:age ratios when they were first observed is not in agreement with Bauer's observations. And conversely, some of our patients with very mild disease exhibited a low value for the height:age ratio at the recognizable onset of their illness. Bauer uses this ratio expressed as a per cent of chronologic age for purposes of comparison. This derived value is subject to such inherent variability, especially when comparing differences between younger and older age groups, that we believe it is unreliable.

We have no ready explanation for the fact that growth increments are higher in *both* groups in the present study between the time of first observation and the end of significant proteinuria. In spite of slight differences in time parameters employed by us and by Bauer, this finding is at variance with his observations. It appears that the greatest acceleration in growth occurs when

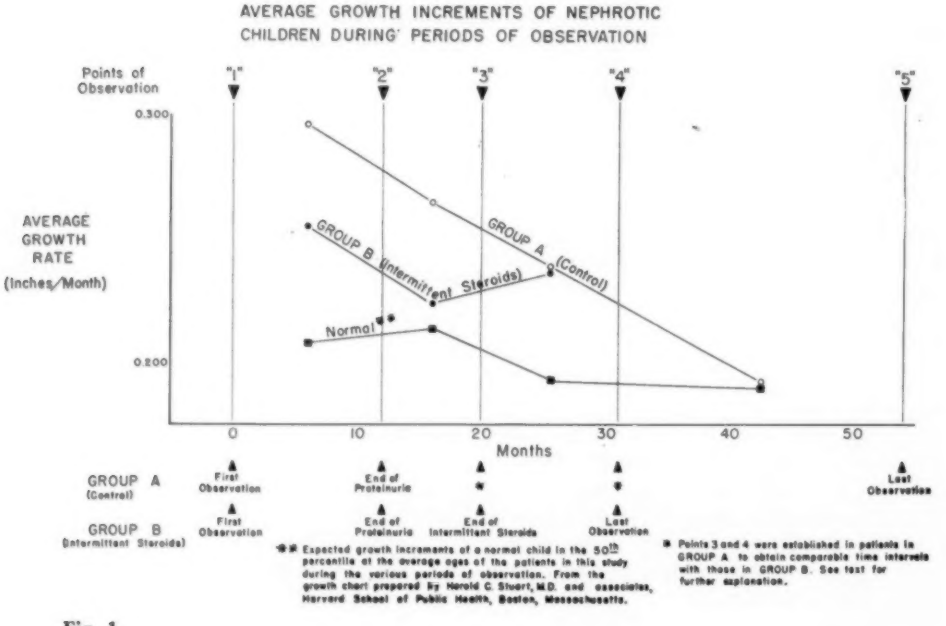
AVERAGE GROWTH INCREMENTS OF NEPHROTIC CHILDREN DURING PERIODS OF OBSERVATION
Points of Observation
"1"
"2"
"3"
"4"
"5"
0.300
0.200
AVERAGE GROWTH RATE (Inches/Month)
GROUP A (Control)
GROUP B (Intermittent Steroids)
Normal
0
10
20
30
40
50
Months
GROUP A (Control)
First Observation
End of Proteinuria
Last Observation
GROUP B (Intermittent Steroids)
First Observation
End of Proteinuria
End of Intermittent Steroids
Last Observation
** Expected growth increments of a normal child in the 50th percentile at the average ages of the patients in this study during the various periods of observation. From the growth chart prepared by Harold C. Stuart, M.D. and associates, Harvard School of Public Health, Boston, Massachusetts.
* Points 3 and 4 were established in patients in GROUP A to obtain comparable time intervals with those in GROUP B. See text for further explanation.

Fig. 1.

Table V. Statural growth rates in children during the course of nephrosis

Interval between points of study*	Group A (control) (inches/month)		Group B (intermittent steroids) (inches/month)		P values
	Average	S.D.	Average	S.D.	
1 to 2	0.296	±0.103	0.256	±0.085	> 0.1
1 to 3	0.297	±0.059	0.242	±0.051	< 0.002
3 to 4	0.238	±0.053	0.237	±0.068	> 0.5

*Point 1, when first observed; Point 2, when significant proteinuria ceased; Point 3, Group B, when intermittent steroid administration ceased and Group A, established to obtain a comparable time interval; Point 4, Group B, when last observed and Group A, established to obtain a comparable time interval.

daily urinary protein losses have begun to fall to low levels.

During active disease the growth rate of a child with nephrosis is inversely related to the activity of the renal disease as estimated by proteinuria. With the advent of remission proteinuria diminishes or disappears. Nitrogen balance then becomes positive[8] and rapid statural growth occurs in an apparent effort "to catch up to the expected height." This rapid spurt in growth may last for an average of 20 months. Steroid therapy to induce and maintain a remission of the disease appears to cause a decrease in the expected nitrogen anabolism and hence retardation of expected growth.

Our observations indicate that when the disease of children with nephrosis is in remission, there is a phase of accelerated growth in height. Intermittent administration of steroids during this phase tends to retard this otherwise accelerated growth rate. We have not had sufficient time to observe whether those who received intermittent steroid therapy will eventually compensate for this added delay in growth and attain a final growth achievement which is equivalent with those who did not receive prolonged intermittent steroid therapy.

Current evidence indicates that the maximal benefits of therapy in the nephrotic syndrome can only be obtained by intensive and at times prolonged administration of steroids.[4] Until there is an answer to the question of possible permanent untoward effects induced by long-term intermittent steroid therapy it would seem important to individualize the management of patients with nephrosis once remission, as judged by no laboratory signs of activity of the disease, has occurred. Present data, including our own, are as yet inadequate for an assessment of the effects of intermittent steroid therapy on the ultimate growth achievements of patients with nephrosis.

SUMMARY

The linear growth patterns of two groups of children with nephrosis were studied. One group received prolonged intermittent corticosteroid therapy to maintain remission and the other group (control) did not. Although the growth increments of each group were accelerated just prior to and following remission, those of the patients receiving intermittent corticosteroid therapy were significantly lower than the growth increments of the control group. These differences in growth rates were no longer significantly different when intermittent corticosteroid therapy was discontinued in the first group. Several aspects of growth changes occurring during the nephrotic syndrome are discussed.

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The effect of hemolysis on the van den Bergh reaction for serum bilirubin

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VARIOUS methods for the estimation of bilirubin in blood or urine are based on spectrophotometric analysis of the sample or upon van den Bergh's application of the Ehrlich diazo reaction.[1, 2] An extensive literature exists on the standardization of the latter method and on the variations which may occur as the result of the protein content of the serum, the acidity at which the reaction is carried out, and the proportions of volatile solvents in the test solution. The significance of several of these features are discussed in recent publications.[3, 4, 5] Opinion of the effect of hemolysis in serum samples on the van den Bergh reaction is varied, however. Some standard texts state that the presence of hemolysis invalidates the test but fail to mention the change produced.[6, 7, 8] Other texts make no mention of the effects of hemolysis or indicate that only "marked" hemolysis has an effect.[9, 10, 11] Still other authors state that hemolysis in serum samples has no effect on the van den Bergh reaction.[12, 13]

Using spectrophotometric methods for estimating serum bilirubin content, early workers recognized the interference caused by small amounts of oxyhemoglobin in the serum examined.[2, 14, 15, 16] Recent studies confirm their findings and provide methods for correcting any existing hemolysis.[17, 18, 19] However, in several recent modifications of van den Bergh's technique, no mention is made of the possible effects of hemolysis in serum samples,[5, 20, 21] in spite of Engel's[22] demonstration in 1939 that the presence of hemoglobin in serum samples reduced the measured bilirubin content. Laurence and Abbott[23] found that hemolysis increased the measured bilirubin level in serum samples in their test system. White and co-workers,[24] however, using the Ducci and Watson modification of Malloy and Evelyn's method, found that hemolysis lowered the measured bilirubin content of their samples.[25]

Hemolysis is rare in blood samples obtained by venipuncture from adult patients. However, observation of heel-puncture samples obtained from infants and presented to our laboratory for determination of bilirubin indicated that gross hemolysis was present in nearly one-third; this experience is apparently shared by White and co-workers.[25] Since consistent opinion on the effect of hemolysis on the van den Bergh reaction could not be found, the following study was undertaken with the hope of providing more data on the subject.

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METHODS

The van den Bergh reaction was carried out according to the method of Kingsley.[26] This technique represents a slight modification of the method of Malloy and Evelyn,[24] differing in the acidity of the test solution and the proportion of methanol to the total test volume. It was the method used in previous studies in our laboratory[3] and offers several advantages as a micro or semimicro technique. Briefly, the method involves the reaction of from 0.1 to 1.0 ml. of serum with 2.0 ml. of diazo reagent prepared exactly in the method of Malloy and Evelyn.[24] Water is added to make a 6.0 ml. test volume and the color development of the "direct" reaction is measured at 1 and 15 minutes. Then 3.0 ml. of methanol is added to obtain a total bilirubin value in a theoretical test volume of 9.0 ml. Thirty minutes are allowed for full-color development in this portion of the test.

Jaundiced sera were obtained by venipuncture from adult patients or from infants with erythroblastosis at the time of exchange transfusion. These samples showed no gross hemolysis and no absorption peaks could be demonstrated at 580 or 540 mμ. Hemoglobin solutions were prepared by washing red blood cells from normal adult donors 3 times with saline; then the cells were hemolyzed, and the stromal lipids were extracted with toluene. The hemoglobin content of the resultant solution was adjusted to a concentration of 4.0 Gm. per cent by addition of distilled water (as measured by a calibrated spectrophotometer). From this stock solution and appropriate dilutions of the stock solution with distilled water, calibrated 20 mm.^{3} pipettes were used to deliver 20 mm.^{3} aliquots of hemoglobin solution to different volumes of jaundiced serum. Samples thus prepared were then reacted with the diazo reagents. Serum volumes used in the reaction ranged from 0.1 to 1.0 ml. Appropriate "blank" nonreactive tubes were maintained for each serum and for each hemoglobin concentration.

All measurements were made on a Coleman Junior spectrophotometer (Model 18-A) at 540 mμ with the use of cuvettes 19 by 108 cm. The spectrophotometer was calibrated periodically against appropriate standards.

EXPERIMENTAL RESULTS

The results of the experiment are presented in Figs. 1, 2, and 3. The "one-minute" and "fifteen-minute" direct azobilirubin color density as well as the total azobilirubin color density is given for 4 of the samples tested at varying hemoglobin concentrations. The results on the samples presented in the graphs are representative of the many examined. The universal pattern seen was a decrease in the measured bilirubin content of the serum sample with increasing concentration of hemoglobin. Variations in the degree of effect existed, however, and there appeared to be no consistency in the pattern between samples. In some samples the reduction in the total azobilirubin color density could be accounted for by the decrease in the measured level of conjugated bilirubin (Sample A, Fig. 1, Sample C, Fig. 3), while in other samples, there was a reduction in measurable conjugated and nonconjugated bilirubin, as shown by the differences in slopes of the direct and total bilirubin curves in Sample B, Fig. 2. In certain samples, the reduction in measured azobilirubin bore a satisfactory linear relationship to the hemoglobin content of the serum (Sample D, Fig. 3), whereas in other samples, the response was clearly not linear. Comparison of the spectrophotometric absorption curves for acid hematin and azobilirubin indicated no coinciding absorption peaks or other possible explanations for the observed effects.

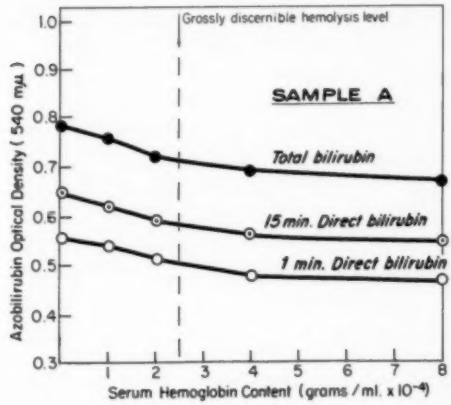
In nonicteric serum samples, hemolysis could be detected by the naked eye at hemoglobin levels of approximately 1 by 10^{-4} Gm. per milliliter. In jaundiced serum samples, however, the discernable level of hemolysis varied between 2 and 3 by 10^{-4} Gm. per milliliter, values comparable to those noted by Davis and Sheard.[16]

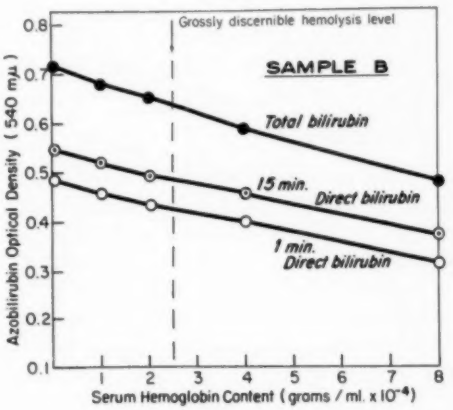
When serum volumes less than 1.0 ml. were used in the van den Bergh reaction,

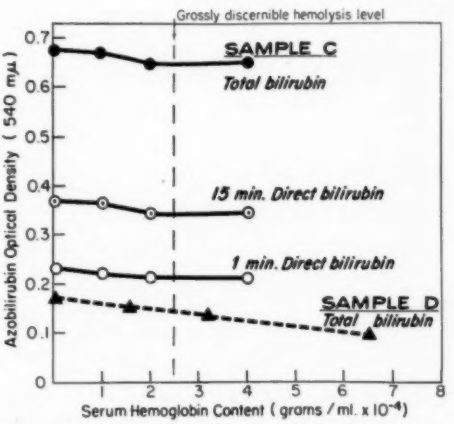
the effect of hemolysis was less than when volumes of 1.0 ml. were used. At serum volumes of 0.1 ml., a slight but consistent reduction in azobilirubin color development was seen. This amounted to approximately 5 per cent reduction at the level of discernable hemolysis, compared with approximately 15 per cent reduction at the same level of hemolysis when a full 1.0 ml. of the same serum sample was used in the reaction.

DISCUSSION

A portion of the variation in the effect of hemolysis on measured bilirubin levels in random serum samples may be explained by differences in the total protein or albumin content of the samples tested. The effect of varying concentrations of protein in the van den Bergh test system is well known.[4, 5, 19] Unfortunately, protein levels were not determined on the samples tested. It is difficult, however, to explain differences in qualitative reaction on the basis of variation in the protein content of the test system. Thus, the fact that a linear response with increasing hemoglobin concentrations was not seen in all samples and the fact that differences in the degree of effect on nonconjugated and conjugated bilirubin could be demonstrated indicate that mechanisms other than the total protein content of the system play a role. A portion of the quantitative effect of hemolysis in a given sample may be explained by the buffering effect of hemoglobin and the resulting change in acidity in the test solution.[3, 4] It is unlikely that this could be the total explanation since the amount of hemoglobin added to each sample of serum was very small and no consistent shift in the acidity of the test solutions could be demonstrated with the pH electrometer employed on several samples where these measurements were made. To date, no adequate explanation for the qualitative differences in the effects of hemolysis on the van den Bergh reaction exists; until such reasons are found, it seems impossible to correct accurately the van den Bergh determination for the presence of hemolysis in serum samples.


Grossly discernible hemolysis level
SAMPLE A
Total bilirubin
15 min. Direct bilirubin
1 min. Direct bilirubin
Azobilirubin Optical Density (540 mμ)
Serum Hemoglobin Content (grams / ml. x 10⁻⁴)


Grossly discernible hemolysis level
SAMPLE B
Total bilirubin
15 min. Direct bilirubin
1 min. Direct bilirubin
Azobilirubin Optical Density (540 mμ)
Serum Hemoglobin Content (grams / ml. x 10⁻⁴)


Grossly discernible hemolysis level
SAMPLE C
Total bilirubin
15 min. Direct bilirubin
1 min. Direct bilirubin
SAMPLE D
Total bilirubin
Azobilirubin Optical Density (540 mμ)
Serum Hemoglobin Content (grams / ml. x 10⁻⁴)

Figs. 1, 2, and 3. Decrease in azobilirubin color density with increasing serum hemoglobin content in 4 representative serum samples. The approximate level of grossly discernable hemolysis in jaundiced sera is noted in each figure.

While the effect of hemolysis is usually small and while it may be minimized by using the smallest volume of serum consistent with the bilirubin level, the fact that hemolysis does have an effect on the measured bilirubin content of serum samples must be appreciated by the pediatrician. With infants, where blood samples are frequently hemolyzed and where the absolute bilirubin level is used as a guide for therapy of erythroblastosis, these variations in the van den Bergh reaction may be of clinical significance. Even though the reduction in measured bilirubin content of a grossly hemolyzed sample may not exceed 10 per cent with a semimicro technique, all reasonable precautions should be taken to minimize the amount of hemolysis incident to blood collection.

SUMMARY

In the van den Bergh reaction, hemolysis in serum samples results in decreased azobilirubin color development and hence in measured bilirubin levels which are falsely low. The reduction in measured bilirubin content of serum samples ranged from 5 to 15 per cent at discernable levels of hemolysis depending on the volume of serum used in the reaction. No adequate explanation for the effects of hemolysis on the van den Bergh reaction could be found. Qualitative as well as quantitative differences in the effects in individual serum samples make correction of the van den Bergh type of reaction for the presence of hemolysis uncertain at the present time.

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"Premature thelarche" and "premature metrarche" followed by normal adolescence

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THE appearance in postneonatal infancy and preadolescent childhood, i.e., between about ½ and 7 to 8 years of age, of either maturing breast tissue or sexual hair is generally recognized as a clinical and endocrinologic entity.[1] The terms "premature thelarche" and "premature pubarche" have been widely adopted to designate the two conditions. Gonadotropic hormone and sex steroid assays have been shown to be on the same very low level as that of average age or height peers. The pathogenetic theory of a premature competence or responsiveness of specific target organs or tissue receptors to the infantile blood levels of estrogen or testosterone has, therefore, been advanced. The source of both hormones in either sex at this age is thought to be chiefly the adrenal cortex.

As early as 1923 Reuben and Manning[2] have described examples of what they called "precocious menstruation" in otherwise completely immature girls. They wrote: "Precocious menstruation may occur in girls from 1 to 7 years of age; it returns regularly every month; there is no leucorrhea; physical development is normal; and there is cessation of menstrual flow at the end of a variable number of months"; after a cycle-free interval of several years, normal adolescent maturation follows. No explanation was given at the time of the puzzling condition but a careful differential diagnosis was worked out between the various causes of vaginal bleeding in immature girls.[3] In the paper just quoted the present writer discussed a personal observation in terms of several alternatives, among them "precocious menstruation" or what one might describe as an isolated premature estrogenic response of the uterine mucosa." He added: "Although the occurrence of such a syndrome is still in doubt it might be worthwhile to watch out for it."

This was done during the last decade, along with an unsuccessful search of the literature for pertinent publications. The result was the case observation presented below which extends over 6 years. The girl's case history, after only 1½ years of study, had been briefly tabulated and illustrated in a 1955 lecture under the somewhat hasty title of "cryptogenic" or "idiopathic sexual precocity"[4] (Fig. 1, *B*). In the perspective of 4 more years of observation, the girl now seems to be an example of that long searched-for condition which, by analogy, may be termed "premature metrarche."

CASE REPORT

Previous history. Leslie C., No. 594429, was born in Chicago, Illinois. on Feb. 2,

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†*Died April 13, 1960.*

1948. The patient is the only child of healthy young parents. Possibly her mother had had a miscarriage at 2 months' pregnancy in 1949. Of notable illnesses in the family there was a benign pelvic neoplasm in the father's mother who underwent a subtotal hysterectomy. The mother's father and mother had "gout" and "rheumatoid arthritis," respectively. Both the father's grandmothers and one or two sisters of his maternal grandmother had diabetes mellitus. Both the patient's parents were rather tall in stature.

The father's pubescence was said to have begun at the age of 12 years. The age at menarche was known in the father's mother (11 years) as well as in the mother (15½ years), her sister (13 years), and their mother (13 years).

The birth history was perfectly normal. The mother experienced vaginal spotting for the first 3 months of gestation. The birth weight was 6 pounds, 10 ounces (3.0 kilograms). The infant was breast fed for 6 weeks and then raised on artificial feeding. Neither nutritionally nor developmentally was there anything abnormal in the feeding history. Her first tooth erupted at 7 months and later dentition was early but not abnormally so. This was also true of neuromotor, personality, and scholastic maturation. Routine immunizations were given up to 1959; the tuberculin test was negative in 1957.

Her record of past illnesses included: successful prevention of measles during infancy; x-ray therapy to the adenoids for recurrent upper respiratory infections with earaches in 1951, followed by tonsillectomy in 1957 (both on outside recommendation); mumps and measles in 1954; chickenpox in 1957 and rubella in 1958. About 1957 it was noted that her left hip was on a higher level than the right when she was standing and walking but there was no limp; a dorsolumbar kyphoscoliosis was present. This was first treated by a built-up heel in the right shoe and, in 1959, by surgical insertion of staples into the right femoral epiphyseal plate (Presbyterian–St. Luke's Hospital, Chicago).

Present history. Before mid-January, 1954, the mother noticed that Leslie's breasts were enlarged to a "puffiness" of about 5 cm. across. Also, the nipples became slightly protuberant and changed in color from pink to dark brown. Late in January slight vaginal spotting was observed, consisting of 2 to 3 drops of brown blood on 2 consecutive days. For the following week, after one day of spotting, a slight colorless mucus discharge was noted. On February 19 more definite spotting with several drops of fresh blood appeared, increasing over the next two days to about 3 to 4 teaspoonsful per day. The blood was dark the first two days and brighter red the third; there was no clotting. Occasional cramps were reported. No pubic or axillary hair was noted. She had not seemed to grow at a higher rate during recent months. There had been no change in personality and behavior lately. She continued to be a quiet, sensitive child who was in no way interested in the opposite sex. An intense and repeated search for estrogen-containing cosmetics or other articles was undertaken and none were found.

Clinical observations from age 6 to 12 years. A graph illustrating the patient's two phases of sexual changes, her somatic growth and her intercurrent illnesses is presented in Fig. 1. Except for the orthopedic condition of her left hip (Fig. 1, *B* and *C*) there were no noteworthy contributory findings, especially none in the central nervous system. The blood pressure was normal throughout (about 98/60 mm. Hg). The chest x-ray, tuberculin and Kahn tests, and routine blood and urine examinations were likewise normal.

During her hospitalization in February, 1954, at the age of 6 and $\frac{1}{12}$ years, she appeared to be a healthy girl of little more than average-size and with a premature mammary development (Figs. 1, *A*, and 2). There was bilateral engorgement of palpable breast tissue 5 cm. in diameter with budding and pigmentation of the nipples. There was no other skin pigmentation. No sexual hair was present. On gynecologic consultation

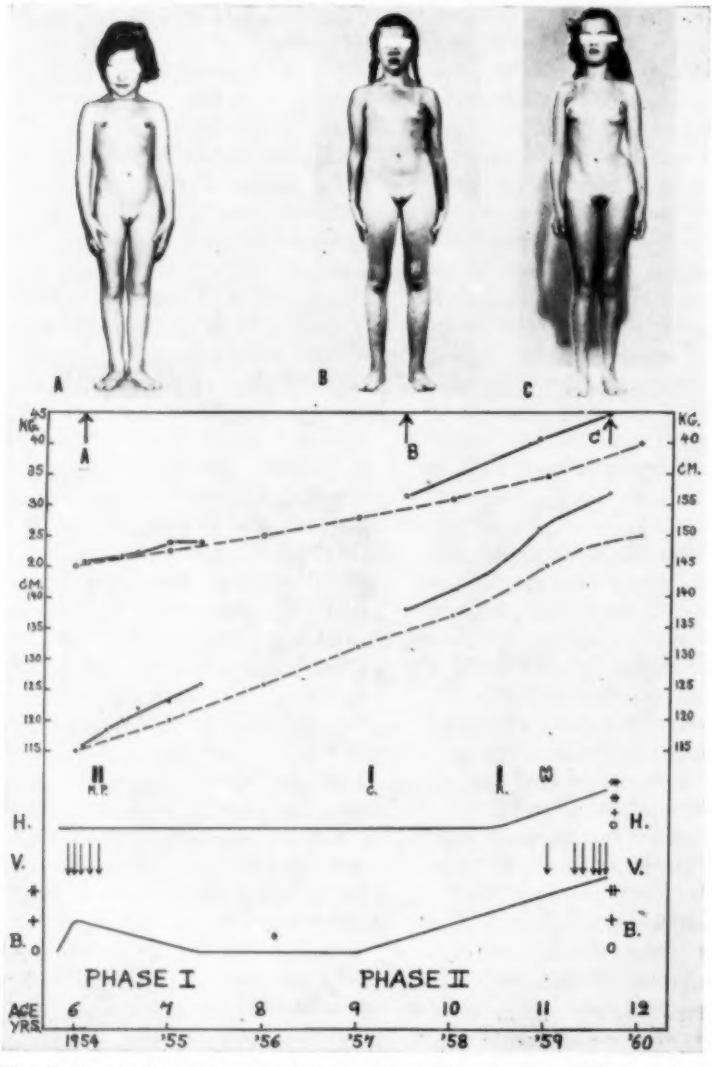

Fig. 1. Graph illustrating sexual changes in Leslie C., aged $5\frac{11}{12}$ to $11\frac{8}{12}$ years. *Phase I*, left, $5\frac{11}{12}$ to $7\frac{4}{12}$ years: Premature thelarche with pigmentation of nipples (curve *B*, photograph *A*) and premature metrarche (left arrows): last vaginal spotting between mumps and measles (bars *M*, *P*). Note absence of pubic hair (zero, curve *H*). *Interphase*, middle, $7\frac{4}{12}$ to 9:0 years: sexually infantile period. *Phase II*, right, 9:0 to $11\frac{8}{12}$ years: early normal sexual maturation (curves *B* and *H*, right arrows, photographs *B*, *C*): note rather pale nipples; no axillary hair at $11\frac{8}{12}$ years. Diffuse goiter of puberty at 11:0 years (thyroid symbol). Somatic growth in weight and height (top curves): Circles, weight in kilograms; dots, height in centimeters; unbroken lines, patient's measurements; broken lines, those of means for girls in Iowa growth charts. *B.* breast tissue; *V.* vaginal bleeding; *H.* pubic hair; *P.* mumps; *M.* measles; *C.* chickenpox; *R.* rubella.

the labia minora appeared somewhat prominent but within normal variation. No abnormal pigmentation of the external genitals was noted. The clitoris was not enlarged. The vagina was small and entirely infantile and contained some blood-tinged fluid. The uterus was likewise infantile in size and no adnexal masses were palpated. Upon vaginoscopy there were no significant changes from the infantile norm and no foreign body was found. Later the same year, when vaginal bleedings had long ceased, a 3-month period of daily morning rectal temperatures showed a swing from 97.8° to 99.0° F. and an average of 98.5° ± 0.5°, except during two mild feverish infections.

Her somatic growth during the 6-year period stayed within, or very near, the plus 1 standard deviation from means for height and weight of normal girls (Fig. 1). Proportionally, at 6 and 1/12 years of age, her symphyseal height related to total height was that of a 7-year-old average girl and her relative arm span that of a 9-year-old girl. Her skeletal age was then normal (6 years). Her dental maturation at ages 6 2/12 and 7 4/12 was partially advanced by about 2 years and at age 10 11/12 by about 1 year; at the latter age she had 28 permanent teeth. Psychosexually she behaved entirely like an immature girl of 6 to 11 years of age.

After discharge from the hospital she had 2 more periods of vaginal spottings, from March 31 to April 1 and from April 24 to 27, 1954. The last spotting occurred between the occurrence of mumps (April 16) and of measles (May 15). There were no more vaginal bleedings at any time until about 5 years later. The breast tissue receded gradually until age 7 4/12 years (mid-1955) and the breasts remained infantile to the age of 8 11/12 years (early 1957, Fig. 1, *B*).

Laboratory studies (1954). A skull x-ray and intravenous pyelogram were normal at age 6 1/12 years. Vaginal smears, taken 5 times between March 15 and 31 and once each in August and October, 1954, failed to show the slightest estrogenic effect (Dr. G. L. Wied). Urinary sex hormone assays late in February, 1954, were reported as follows (Dr. G. M. Riley, University Hospital, Ann Arbor, Michigan): "We could demonstrate no estrogen in the 24-hour specimen. The follicle-stimulating hormone test was negative at 6 mouse units per day. These results are normal for a child of this age." At the same time, two 24-hour urine specimens of 515 and 650 c.c. yielded 0.26 and 0.23 mg. of creatinine, respectively, and 1.6 mg. of 17-ketosteroids, likewise normal for a 6-year-old child. An attempt to determine urinary pregnandiol failed for technical reasons.

If the brief period of temporary premature sexual changes early in Leslie's life is called "Phase I" then, after a sexually neutral interval of about 1½ years, "Phase II" began early in 1957, at 8 11/12 years of age, with what is known as "early normal" sex maturation. It consisted at first of budding of breasts and nipples (Fig. 1, *B*). However, this time the nipples were less pigmented and remained rather pale to age 11 8/12 when the breasts were well formed (Fig. 1, *C*). Pubic hair appeared first in mid-1958, at age 10 4/12 years, and axillary hair shortly thereafter. The menarche occurred in February, 1959, at 11 1/12 years (Fig. 1). The first menstrual period lasted from February 28 to March 2, 1959; that same year menstrual periods reappeared on June 29 lasting 9 days, on July 27 lasting 8 days, on August 23 lasting 9 days, on September 12 lasting 6 days, and on October 30 lasting 4 days; intervals measured 4 months, 28, 28, 21, and 19 days, respectively. Between 9½ and 11½ years the usual early adolescent growth spurt took place (Fig. 1). Shortly before the menarche a soft diffuse swelling was noted in front of her neck. On 2 examinations one year apart this goiter proved to be adolescent in type with no nodules in the substance of the gland and no palpable regional lymph nodes (there had been radiotherapy of the adenoids at age 3). Thyroid extract in doses of ¼ to 1½ grains (15-90 mg.) per day was administered since January, 1959.

She was last seen in excellent health on Oct. 20, 1959.

DISCUSSION AND COMMENT

As indicated earlier, a diagnosis of "cryptogenic" sexual precocity was at first entertained.[4] When vaginal bleedings ceased following the measles infection, the faint possibility of a complicating oophoritis was discussed. However, about 6 months later, when the girl was again seen in the Clinics at 6½ years of age, doubt first arose in regard to that diagnosis. Vaginal bleedings had altogether ceased, the breast tissue and the mammillary pigmentation had clearly regressed, sex hair had failed to make its appearance, and there was no noteworthy somatic growth spurt. The possibility of "premature thelarche" was then first suggested, although the nipples seemed rather deeply pigmented; also, no vaginal bleeding had so far been reported to be associated with it. However, the laboratory studies seemed to agree with the assumption of premature thelarche.[1]

Fig. 2. Photograph of Leslie C., aged 6½ years, showing torso in half-profile with premature thelarche.

On the other hand, all findings or lack of them argued against both true precocious puberty and exogenous estrinization. In either condition one would have expected a down, or even definite growth, of pubic hair, a degree of palpable uterine enlargement, and an estrogenic response of the vaginal epithelium. In the case of precocious puberty[1, 5] a somatic growth spurt and advanced skeletal maturation would also have occurred and, in the case of extraneous estrogen intake,[6, 7] skin areas other than that of the nipples might have appeared pigmented.

At the time when premature thelarche was first suggested, Reuben and Manning's early report on "precocious menstruation" was also brought to mind.[2] The authors had described it as an isolated phenomenon, without any other estrogenic response such as mammary engorgement. In the same manner, later on, "premature thelarche" was defined as an isolated sign not accompanied by vaginal bleeding.[1] However, there did not appear to be any serious theoretical objection to an occasional combination, in the same girl, of both these estrinization phenomena. In the absence of laboratory evidence of abnormally increased estrogenic activity, it was natural to assume that both mammary tissues and uterine mucosa had prematurely and temporarily responded to the normally subliminal traces of circulating estrogens derived, even in a completely immature girl, from the cortex of the adrenal gland.[1] Because of the less than monthly ("men"-strual) cycles of the scanty vaginal bleedings and in order to stress the purely local response of the mucosa of the uterus ("metra"), the term "premature metrarche" rather than "premature menstruation" was here introduced. The fact that, in spite of failing evidence of cyclic estrogen production, there was in this girl a certain "menstrual" rhythm of bleeding [as there is in stimulation by ovarian estrogenic neoplasms][8] might tenta-

tively be ascribed to an inherent cyclic responsiveness of the endometrium. With this, conceivably, the toxins of the measles may have interfered at the time of cessation of vaginal bleedings.

As time went on, more and more support accumulated for the notion of a combined premature thelarche and premature metrarche. In the first place, a more than 1½-year-long interphase of complete abeyance of sexual characteristics succeeded Phase I of the girl's sexual changes. During that neutral interval, somatic growth appeared to have continued at the same rate as before. There was no change, either, in regard to the child's environment, particularly to the mother's cosmetic practices. Second, during the following 4 years, between ages 9 and 12, Phase II of her sexual changes was observed which consisted of an "early normal" sexual maturation.

Phase II was entirely regular with respect to expression and sequence of sexual phenomena. Breast tissue began to grow at 9 years and sex hair at 10, followed by the menarche at 11. This corresponded to the onset of puberty on the part of the father at 12 years and that of his mother at 11.[9] The pigmentation of the nipples was less intense during Phase II than it had been during Phase I. She experienced a normal (pre-) adolescent growth spurt and her denture was complete at the age of 11. Her psychosexual maturation corresponded likewise to her chronologic age. The goiter was that observed customarily in adolescents; there was no indication of thyroid cancer inspite of a history of pharyngeal irradiation.

SUMMARY

A case report is presented of a healthy girl who, between 6 and 12 years of age, experienced 2 phases of sexual change with a silent interval between them. Phase I lasted from 6 to 7 11/12 years of age and was characterized by an isolated subliminal estrogenic response of mammary tissues and uterine mucosa. The latter response, consisting of irregular vaginal bleedings, occurred only during the first 3 months and ceased following an infection with measles. This phase was termed "premature thelarche and metrarche." The absence of sexual hair growth, of a somatic growth spurt, of positive estrogen laboratory tests, and of any other demonstrable cause for the premature vaginal spottings appeared to confirm the diagnosis. There followed an interphase, from 7 11/12 to 9 years, of complete absence of all sexual phenomena. Between 9 and 12 years a perfectly regular picture of "early normal" adolescent maturation was observed, with the menarche at 11 years of age (Phase II).

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Self-feeding in infancy

Charles Hendee Smith, M.D.*

PRINCETON, N. J.

TWENTY years ago I watched a young mother† feeding her baby of 4 months by a method which she had devised herself. It was obvious that she had found something new and fundamentally different from the way in which babies usually were fed. I adopted the method at once, and since have taught it to all the mothers of babies in my practice by the middle of the infant's first year. It is uniformly successful if it is used with intelligence.

The first step is to train the baby to hold his own bottle, at about 4 months of age, when he is able to use his hands for voluntary grasping. A baby who holds his bottle can be easily trained to hold his cup. The "sissies," who will not take a bottle unless it is held for them, learn the use of a cup less readily. Orange juice may be taken from a cup at about 2 months and milk by the middle of the first year. Of course, the plan of giving a cup for all feedings from birth, never using a bottle, has its advocates, but it has disadvantages. It is more difficult to feed a baby with a cup in his first weeks, it is harder to get a full feeding down, and it takes longer than it does to give a bottle. In the first half year, at least, it is easier to give a bottle, but all babies should be trained to the cup before the end of the first year. The longer a baby is allowed to have a bottle the harder it is to wean him from it. Babies who take the bottle into the second, or even into the third, year are apt to get jaw deformities from the protracted sucking. This is a common cause of dental malocclusion, the pressure on the jaw being greater when all the incisors have erupted. Moreover, persistence of sucking, an infantile activity, interferes with normal development into childhood.

The kind of cup makes little difference. Some mothers have better success with a training cup, which has a small projection at one side, such as a spout. Some babies take a small glass or cup better than the standard size. Various receptacles may be tried, with the one being used which works best. In starting the cup the baby's hands should be held around it, so that he has a feeling of helping. The mother should sit at the baby's right side as in spoon feeding. Soon the baby will hold the cup alone.

As soon as solid foods are started, at about 4 months of age, the baby should be taught the purpose of a spoon. Earlier feeding of solids, which has enjoyed a great popularity of late, has no special advantages. The small amounts which a young infant will take have no great nutritional value; if too large a quantity of solid food is forced, part or all of the bottle may be refused. There is some reason to think that forcing solids too early

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†*Mrs. Mary Hendee Smith, to whom I am indebted for the underlying principles of this method.*

may account for an antipathy to them later on. To give a spoon to the baby, and to expect him to discover himself how to use it, does not suffice. He must be taught how to use the spoon correctly.

At first, when the baby is about 4 months old, the mother holds him on her lap, with his back against her body, her left arm around him controlling his left arm, and with the bowl of food in her left hand. She takes the spoon in her right hand, holding it with her thumb and first 2 fingers. The baby's hand is placed around her little finger and is held in contact with it by her ring finger. The baby will soon grasp her finger firmly (Fig. 1). She then puts a small amount of food on the spoon and conveys it to the baby's mouth. If the food is palatable and the baby likes it, he will soon begin to pull on the mother's finger to get it. It is amazing how quickly the lesson is learned; in a few days the baby is practically feeding himself, aside from filling the spoon, which is learned more slowly. No force should be used at any time. If the baby resists the feeding process, it should be given up for the day and tried again a few days later. The best food to begin with is a pleasant tasting cereal sweetened with a little sugar. Some of the much-advertized cereals have a taste which is far from pleasing to most adults. The mother should taste the cereal and see how she would like it herself. Cooked fruits are slightly acid and may be refused, unless the baby has been accustomed to taking orange juice.

Soon the baby will be old enough to sit in a high chair. The mother must sit at his right side, her left arm around him and her left hand holding the baby's left arm just above his left elbow. Her left forearm supports the baby's back; her hold on the baby's arm prevents him from trying to use his left hand in the feeding process. Babies are two-fisted individuals and try to use both hands in attacking any problem. The baby holds the mother's little finger, as described above (Fig. 2).

At 5 to 6 months the spoon should be put into the baby's hand, but the mother has to guide his hand and help him fill it. Until he learns the scooping motion of filling the spoon he cannot feed himself without help. If he tries it alone too early, he merely beats the food with the spoon and becomes exasperated because he cannot fill it. Learning to get food into the spoon and to convey it to his mouth efficiently usually takes a couple of months. Some spilling must be expected; a large bib catches most of it, but a square of oilcloth on the floor under the chair saves the rug or carpet. Some mothers become discouraged by the spilling and abandon the attempt at training. They must be told that the time saved later, when the baby can be independent of help, more than compensates for cleaning up a little spilled food. The psychological reasons for making a baby independent of his mother as early as possible

Fig. 1. Baby 4 months old fed on mother's lap. The baby grasps the mother's little finger and pulls on it to bring the spoon to his mouth. The mother holds the bowl of food in her left hand and can control the baby's left hand with her wrist if necessary.

Fig. 2. Baby of 5½ months fed in high chair. The baby holds the mother's little finger. She holds his left hand and supports his back with her forearm.

Fig. 3. Baby of 5½ months. For the first time the spoon was put into his hand. Before this he had held on to his mother's finger. He at once put the bowl of his spoon into his mouth, as if he had been doing it for a long time. Note the position of his hand on the curved spoon handle.

must be emphasized. The baby is somewhat more apt to fight the mother's help after the spoon is put into his own hand. If he stiffens his arm and refuses to let her guide him, she should use no force but coax him into letting her fill the spoon and allow him to put it into his mouth by himself. He will soon find out that he cannot fill the spoon alone and will accept the needed help (Figs. 3 and 4). Fig. 6 shows the opposite situation. The baby of 10 months had been helped by his mother, but he was becoming so efficient that she was told to let him try it alone. He held out the spoon toward her hand, his whole attitude saying, as plainly as if with words, "Help me a little longer, Mother!" A week later he refused all help and fed himself alone thereafter.

The spoon used may be an ordinary teaspoon, preferably a cheap one, the handle of which easily can be bent into a curve. The baby grasps the spoon near the end. As he brings the spoon toward his mouth he tends to supinate the hand somewhat; with a straight spoon more spilling results (Fig. 3). The small baby spoons with a curved handle, usually presented by loving relatives or friends, are not as good as a bent teaspoon for they are too short.

The mother who sits facing the baby cannot control either of his hands. Fig. 10 shows the usual result. This baby wants to use his hands; his attitude clearly shows it, but the mother cannot put the spoon into the baby's right hand unless she holds it in her left, and filling it would be awkward or impossible.

Left-handed babies present a special problem. If a baby refuses to hold the spoon in his right hand and habitually reaches for objects with his left hand it may be that he is congenitally left-handed. A family history of one or more left-handed relatives increases this probability. The mother may try sitting on his left side and guiding the spoon in his left hand with her left, which is somewhat awkward. The effort to make him use his right hand should not be abandoned without a thorough trial. Many left-handed individuals learn to use the right hand at the table in the conventional manner

to save themselves embarrassment. If the baby absolutely refuses to use his right hand it does no great harm to let him use the left, although it is somewhat more difficult for a right-handed mother.

Once the training in self-feeding is started it should never be abandoned. If the baby finds that his mother will feed him when he objects to helping himself, he is likely to let her do it. Every time she gives in, thinking that he must get the food somehow, she makes it harder the next time. She can easily make the baby understand that he must help if he wants to get the food.

A method sometimes recommended is to give the baby one spoon, when he is able to use it, and to have the mother partially feed him with another spoon. The usual result is that the mother does most of the feeding. The baby has no incentive to increase his own skill, finding it easier to lean on his mother. It is just as easy and just as quick for her to guide the spoon in the baby's hand as it is to let the baby be wholly passive while she shovels the food into him. The mother often tries to feed the baby too fast, for she is usually in a hurry. If the spoon is in the baby's hand, he can control the rate of feeding by offering some resistance when he is not ready for the next mouthful. The baby in Fig. 5 had another plan. If he was not ready for more he simply turned his head away.

By the training method described, babies can be taught the use of cup and spoon by the age of 8 or 9 months, if started by the middle of the first year. Even if the training begins later the baby should be independent of help before he is a year old. Figs. 7, 8, and 9 show a boy of 9 months who had been feeding himself for several weeks. He was watched and photographed during a meal at which he took a bowl of cereal, a bowl of cooked fruit, and 2 cups of milk without any help and with only a small amount of spilling. The baby needed no help after 10 months.

On the other hand, writers on child development state that self-feeding is not efficient until much later.

Bakwin and Bakwin[1] state that training to a cup may be started at 8 to 12 months and the bottle discarded at about a year. At 12 to 14 months and often earlier the infant may be taught to manage a spoon. Spilling is inevitable whenever training is started. By

Fig. 4. Boy of 10 months feeding himself efficiently with only the slightest guidance by his mother. She holds his left hand lightly, but it is not really necessary, for he no longer tries to use it. Note the large bib to catch any spilled food. The hot water plate keeps the food warm.

Fig. 5. Mother has tried to feed him too fast. He turns his head away until he is ready for the next spoonful.

2 years of age the baby can be taught to feed himself efficiently and neatly.

Bartram[2] says that a baby can hold a bottle at 6 months and a cup in another 2 to 3 months. He may have a spoon as soon as he can hold it, at 10 to 12 months, and should be largely responsible for his feeding by the end of the second year.

Hughes[3] states that a baby may be able to put his hands about a bottle at 4 months. After many patient efforts he learns to be skillful with a cup at about 1 year, but not until 18 months does he begin to be competent with a spoon.

Holt and McIntosh[4] say that the cup may be started at 9 to 10 months and that the baby should take all his milk from a cup at 1 year. The use of the spoon should be taught as soon as possible, sometimes by the end of the first year.

Gesell and Ilg[5] state that it is possible for an infant to imbibe a cup of liquid in the first quarter year if he is aided by skillful manipulation. At 36 to 40 weeks he may hold a cup for a brief period; 1¼ years is the typical age at which self-management makes its first appearance. Spoon feeding begins at about 3 months with the infant in the mother's lap. At about 6 months he sits in a chair. Toward the end of the meal he may reach for the dish or grasp at the spoon. At 9 months he takes the food better if he has something to play with, such as an empty spoon. In the second year self-help is characteristic, though some children let themselves be fed through the year. Spilling is marked at 15 months, moderate at 18 months, and tends to disappear at 2 years.*

Aldrich and Aldrich[6] believe that by the second year we find it hard to let a child profit by the rapid motor growth that he started in the first year and learn the handling of his own cup and spoon. It is clear that he can master them only through his own efforts; no one can do it for him. Yet it is almost impossible for an adult to watch a young child juggling the cup and spoon without an irresistible impulse to help him

Fig. 7. "Bottoms up" at 10 months. The same baby is shown in Figs. 4, 5, and 6.

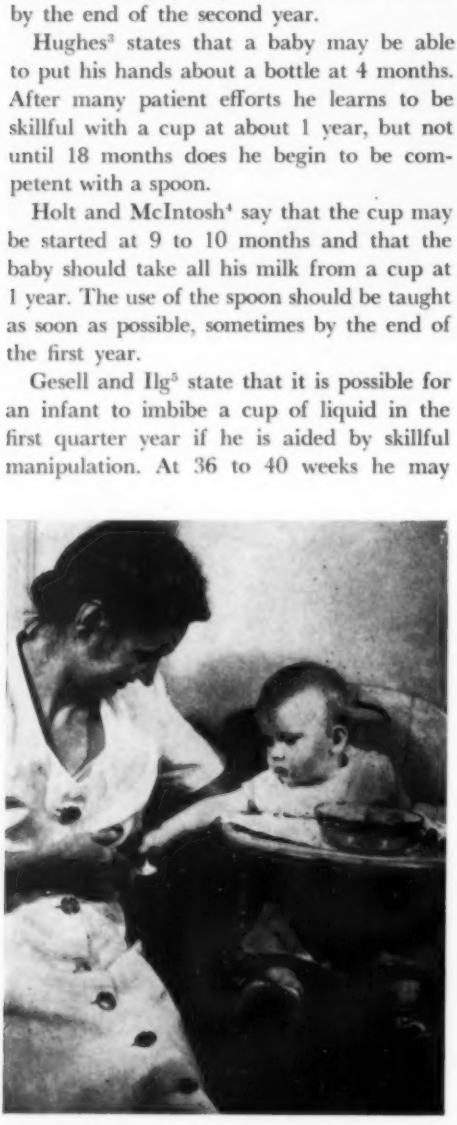

Fig. 6. Mother took her hand away to see if he was ready to go it alone. The baby is asking her to help him a little longer. In another week (at 10 months) he refused all help.

*All of the photographs in Gesell and Ilg show the mother facing the child in the chair and holding the spoon with the baby's hands free. None of them show the mother guiding the spoon in the child's hand.

out. Too much help only puts off the arrival of his own self-sufficiency. Probably the real objection to this trial and error method is its untidiness. One of the surest ways to encourage satisfactory eating habits is to recognize that children need to use their own bodily equipment and become masters of their own meals. It is not at all uncommon to see a mother anxiously spoon feeding a 6-year-old who is well equipped muscularly to handle a baseball bat or even to write his name.

All these statements are true enough, except that with a little guidance in the first year the baby does not juggle the cup and spoon in the second and no longer needs help. To give a baby a spoon and make him work out his own method of its use starts him off no better than the first babies in the world and robs him of knowledge gained by all the experience of mankind. It is like giving a small boy a tennis racket and turning him loose on the court without showing him the correct form of the tennis stroke. He will learn to play in time after a fashion, but he will play badly and may never rid himself of the bad habits he acquires in teaching himself. A few lessons about the correct way to hit the ball will help him to play well more quickly, and he will always have a better game if he starts right. As a matter of fact, the correct way to use a spoon is much like the form of a good forehand drive.

Is it worth while to train a baby to feed himself in the first year? Twenty years of experience in teaching the method to all infants seen in private practice have proved that it can be done by any cooperative mother. They are all enthusiastic about the results, especially those who have had other children whom they have had to feed every mouthful of food for 3 to 5 years. One of the chief causes of anorexia in the early years is due to feeding by the parent. The child finds out that refusing to eat what the mother offers will upset her and will increase the amount of attention he will get. Babies who learn self-feeding in the first year do not develop behavioral anorexia.

Fig. 8. Boy of 9 months who had been feeding himself without help for several weeks. Note the large bib. His mother stood by while he was eating to rescue spilled food with a pick-up spoon. He finished a serving of cereal, another of cooked fruit, and a cup of milk without any help, except to put the food before him. (Reproduced with permission from Nelson, Waldo E: Textbook of Pediatrics, ed. 4, Philadelphia, 1953, W. B. Saunders Company.)

Fig. 9. The same boy of 9 months as shown in Fig. 8 finishing his meal.

Fig. 10. The wrong way to feed a baby. The mother, who sits facing the baby, cannot control either of his hands. From her expression, whether she gets the food into the baby's mouth is evidently a question of hit or miss. The baby looks as if he would like to use his hands if he could. (Reproduced by permission of *Life* Magazine, the mother, and Nelson, Waldo E.: Textbook of Pediatrics, ed. 4, Philadelphia, 1953, W. B. Saunders Company.)

The time saved by the baby who feeds himself is needed and appreciated by the busy mother. All she has to do is to put the food before the child, instead of having to sit down and coax him to let her feed him for a half hour or more at every meal.

Getting the baby off the bottle saves much time also, for washing and sterilizing bottles is no small task. From the baby's side of the matter, bottle feeding too long often keeps him from taking enough solids, prolongs an infantile performance, and may deform his jaw from the abnormal pressure of sucking. The last of these dangers is increased by the pernicious habit of having the bottle to suck in bed as the baby goes to sleep; this habit is common among babies who are allowed to have the bottle into the second or later years.

CONCLUSION

Babies can easily be taught to feed themselves with cup and spoon in the first year. The essential part of the technique is the relative position of the baby and mother. The mother must sit at the right side of the baby, her left arm behind him, and her left hand controlling the baby's left hand. Her right hand is then free to guide the spoon in the baby's hand. If she sits opposite him she cannot control either of his hands.

It is worth while to train the baby early because it helps free him from dependability on his mother. Anorexia due to the desire to get attention is less likely to develop in the early years if the child feeds himself.

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Recurrent small bowel volvulus in the newborn infant

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THIS paper presents a brief review of the experience with volvulus of the small bowel in children admitted to the St. Louis Children's Hospital from 1935 through 1956, a report of a recent case, and the use of an intraluminal intestinal splint in complicated abdominal surgery in the newborn.

In the period covered by this study there were 21 cases of volvulus of the small intestine (Fig. 1). Of the 21 cases, only 3 (Table II) had associated malrotation of the colon with or without duodenal obstruction. There has been a tendency in the literature to associate volvulus of the small intestine in infants with malrotation of the colon; this is not correct. For although malrotation can occur with or without duodenal obstruction, all cases of volvulus resulting in obstruction of the small intestine are not associated with malrotation of the colon. Sawyer and Spencer[1] reported 18 cases of volvulus; in 10 malrotation was not co-existent. Moretz and Morton[2] reported 36 cases of volvulus without malrotation of the colon. Marrow and Judy[3] reported 8 cases without duodenal obstruction.

Volvulus of the small intestine is presumably related to a faulty posterior fixation of the mesentery manifested by a narrow attachment of the superior mesenteric artery. This failure may or may not be associated with malrotation of the colon.

Table II lists the causes of death in our series. The high incidence of death due to vascular collapse secondary to venous obstruction merits a comment here. When the volvulus is sufficient to produce only venous obstruction without arterial obstruction, there occurs pooling of the blood in the mesentery and the gut with resulting rapid decrease in circulating blood volume and vascular collapse. It is then extremely important to make this diagnosis as early as possible (Table III), as evidenced by the death of 4 patients within 24 hours and of one at 32 hours. The early recognition of shock without obvious bleeding should make one aware of the possibility of volvulus with venous obstruction. Frequently there is little evidence of abdominal pain in the affected infant.

CASE REPORT

H. M., a 12-day-old white male, was admitted to St. Louis Children's Hospital on Jan. 13, 1958, for persistent vomiting. The mother was delivered at term after a normal pregnancy; the birth weight was 6 pounds,

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10 ounces. The mother and child were discharged on the eighth postpartum day. The child did well until the day prior to admission when vomiting began and persisted with the loss of all of the intake.

Examination revealed an active baby boy with good color and an excellent cry. Physical examination was essentially negative except that of the abdomen. In the upper abdomen there were prominent, large gastric waves moving from the left upper quadrant into the right lower quadrant. The upper abdomen was slightly distended.

Laboratory data on admission were: hemoglobin 19.5 Gm. per cent, hematocrit 40 per cent, white blood count 10,000 per cubic millimeter, the differential count normal, and urinalysis negative. An x-ray of the abdomen with a barium swallow was obtained which showed air fluid levels in the stomach and superior duodenal angle. There was no evidence of gas distal to this point, except for a little faint mottling in the left lower quadrant. A barium swallow showed peristaltic waves transversing the stomach from the left to the right. The barium progressed down the duodenum to the third portion and no barium progressed further than the inferior duodenal angle. The preoperative diagnosis was malrotation of the colon with duodenal obstruction due to obstructing bands.

The abdomen was explored through a right rectus muscle retracting incision. The distal small bowel was bluish in color. The infant had a volvulus of a counterclockwise nature with a 220 degree rotation. The volvulus was reduced with ease; there was immediate return of good color to the bowel

Fig. 1.

Table I. Associated lesions and abnormalities

No. of cases	
1	Adenomatous polyp of small intestine
3	Malrotation of the colon
1	Necrotic granuloma of liver
1	Esophageal stricture
1	Atresia of ileum
1	Intra-abdominal hernia
1	Meckel's diverticulum with attachment to abdominal wall
1	Mesenteric cyst

distally. Postoperatively, the child remained on nothing by mouth for 48 hours, and then was started on dextrose, Amigen, K-salt, and a weak milk formula. The child tolerated the feedings well until the twenty-first postoperative day at which time he began vomiting a quarter to half of his feedings. The following day he vomited all of his morning feedings and it was noted that the abdomen was distended. Bowel sounds were adequate. A flat film of the abdomen was obtained and showed several distended small loops of bowel with air-fluid levels. The child was placed on nasogastric suction. Within 24 hours there was no improvement and surgical re-exploration was decided upon.

At the operation the child was found to have a recurrent volvulus, involving the distal one-third of the small intestine with an area of gangrene at the terminal ileum measuring 15 cm. There was no apparent perforation. A resection of the gangrenous ileum was performed and an end-to-end two-layer anastomosis with fine silk was performed. A long tube interluminal splint was then inserted from the ligament of Treitz through the anastomosis and ileocecal valve and into the right colon and brought out through a small wound in the left upper quadrant. The enterostomy was secured to the anterior abdominal wall with interrupted fine silk sutures through the omentum. Postoperatively suction was applied to the interluminal splint with irrigations of saline solution every 2 to 4 hours. On the third postoperative day the child was started on dextrose, Amigen, and K-salt by mouth with

only gravity drainage to the enterostomy interluminal splint. The child tolerated these feedings well and the formula was rapidly increased to full strength by the tenth postoperative day.

On the twenty-first postoperative day the interluminal splint was shortened and removed slowly over the next 2 days. The child's postoperative course was uneventful; the enterostomy opening closed rapidly without sequelae and the child was discharged from the hospital on the sixty-third hospital day.

COMMENT

This case demonstrates one of the major problems in pediatric abdominal surgery (Table IV): the postoperative obstruction caused by peritoneal adhesions with or without compromise of the blood supply and perforation. This problem is all too common in intestinal atresia, meconium ileus, volvulus, and obstructive perforations. Gross[4] stated that, in atresia, postoperative adhesions were responsible for approximately three-fourths of their failures. This is in agreement with the findings of others; whenever there is peritoneal contamination, excessive bowel handling, or excessive blood left free within the abdominal cavity, adhesions will occur and so will their grave complications. Perry[5] found that in the age group under 1 year, 16.7 per cent of the deaths resulted from postoperative obstruction due to adhesions. Gerrish[6] emphasized the importance of the enterostomy tube in proximal decompression to cover the period of decompensation of the bowel and to allow an earlier return of normal peristaltic movement. His excellent results with intestinal atresia are evidence of the validity of this concept. Miller[7] emphasized the importance of the proximal enterostomy tube to take tension off the suture line.

It has often been said that enterostomy tubes in the small intestine should not be used as they function poorly and are associated with complications. With what has just been said above, and with our own findings, we strongly disagree with this statement. When properly used, the long tube intraluminal enterostomy is a lifesaving tool for the surgeon. In 1937 Noble[8] described his plication operation for intestinal obstruction. White[9] reported good results in 16 patients with the use of the intraluminal intestinal splint.

Bricker[10] of the Department of Surgery of Washington University has for the past year used a long rubber intraluminal enterostomy tube in pelvic eviscerations; he reports a reduction of almost 100 per cent in the incidence of postoperative obstructions. A review of recent literature failed to show the use of the long intraluminal splint in newborn infants. In the long intraluminal enterostomy splint we have combined all three important factors that have been emphasized individually: (1) proximal decompression;

Table II. Causes of death

No. of cases	
2	Perforation with peritonitis
5	Vascular collapse second to venous obstruction
1	Postoperative obstruction second to adhesion
1	Died on the operating table—combination of 1 and 2 above

Table III. Time of death after admission

	No. of cases
24 hours or less	5
2 days	1
3 days	1
4 days	1
8 days	1
Total	9

Table IV. Surgical complications

	No. of cases	*Survival*	*Death*
Evisceration	1	1	
Postoperative obstruction from adhesions	3	2	1
Bowel resection	5	4	1

(2) intraluminal guide; (3) nonsuturing plication of the bowel by postoperative planned adhesions. To date we have used the intraluminal splint in 3 children with good results. In the newborn infant, a No. 8 soft rubber Levine tube is used with multiple perforations so that adhesions to the intestinal wall do not occur. The tube is inserted from the proximal jejunum through the ileocecal valve into the right colon. In the newborn infant there will be no difficulty in threading the tube down the intestinal tract, but in the older children the use of a flexible metal or plastic guide, such as an intraluminal vein stripper, will often be helpful. The proximal end of the tube is brought out after the method of Witzel. The tube should be brought through the omentum and anchored to the parietal peritoneum with interrupted fine silk sutures. The postoperative care consists of intermittent suction at a pressure of less than 90 mm. Hg with irrigation of 5 to 10 c.c. of saline solution every 2 hours until peristalsis has returned and the infant is passing flatus. Suction is then discontinued and the splint is left in place for about 3 weeks; the practice of various surgeons ranges from 14 to 48 days. The tube should be removed slowly over a period of 2 to 3 days to prevent retrograde intussusception of the small intestine. The intraluminal long enterostomy tube has been used with success in cases of obstruction with perforation and peritonitis, intestinal atresia, and volvulus. We feel it is indicated in infants whenever there has been soilage of the peritoneum and irritation of the visceral peritoneum as is so common in atresia, meconium ileus, and other intra-abdominal obstruction with perforation.

We have had no complications with the long tube, but a word of caution seems warranted. We feel that the most important single factor is a good closure about the tube and adequate fixation to the abdominal wall. Should a leak occur at the exit of the enterostomy tube, it need not be a major problem, for constant suction at the skin level will provide self-closure and healing.

CONCLUSION AND SUMMARY

1. The experience with 21 cases of volvulus is reviewed, and a report of a case of recurrent volvulus is presented.

2. The use of the long intraluminal splint in the newborn infant is described with the indications for its use. Internal fixation allows controlled adhesions and early feeding.

3. Intraluminal splinting has been used in 5 infants with satisfactory results.

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Congenital tuberculosis

Report of a case

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IN 1950 Amick and colleagues[1] reviewed the literature and reported 124 cases of verified congenital tuberculosis and added 4 cases of their own. Since that time there have been 29 additional ones reported for a total of 157 cases. Of this total figure, 15 were reported in the American literature.

CASE REPORT

A girl weighing 1,720 grams was delivered on June 28, 1959, of a 22-year-old Negro woman who had had 3 previous pregnancies. The expected date of confinement was Aug. 21, 1959. The infant's condition at birth was described as good and the initial physical examination revealed no abnormalities except an umbilical hernia. She was separated from the mother immediately after delivery and kept in the Premature Nursery and had no further contact with the mother in accord with our policy in the care of premature infants. She was started on feedings of glucose water at 18 hours of age and on feedings of house formula on the second day. Feedings were taken and retained and the infant continued to be active with a normal physical examination until the eighth day of life when she appeared listless and did not nurse well. On the ninth day she had an axillary temperature of 100.8° F.

On the eighth day it was called to the attention of the pediatric staff that the mother had a fever of undetermined origin. On the seventeenth day, because of recurrent listlessness and a second elevation of temperature, blood and nasopharyngeal cultures were obtained on the infant despite no other evidence of infection on physical examination and no history of vomiting. The white blood cell count was 15,050 with 34 stab forms, 37 lymphocytes, 6 monocytes, 22 polymorphonuclear leukocytes, and 1 juvenile form. The packed cell volume was 47. Penicillin and streptomycin were started on the day the cultures were obtained because of the possibility of an occult infection.

On the twenty-second day of life, the temperature again rose to 100.4° F. (axillary) and for the first time hepatomegaly and splenomegaly were noted. Chloramphenicol was added at this time to the therapy of penicillin and streptomycin.

Within the next few days the infant developed cervical, axillary, and inguinal lymphadenopathy. She continued to have elevations of temperature up to 101° F. (axillary) at intervals up to the forty-eighth day. The liver was palpable 4 cm. below the

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right costal margin and the spleen was palpable 4 cm. below the left costal margin.

On the twenty-fourth day of the infant's life the mother was found to have miliary tuberculosis. Consequently, a spinal tap was done on the infant and a specimen of bone marrow was obtained for smear and culture. First strength PPd at this time was negative. Because of the mother's history and the infant's clinical course, antituberculous treatment consisting of Isoniazid 40 mg. per kilogram intramuscularly and streptomycin 50 mg. per kilogram were begun. Penicillin and chloramphenicol were discontinued at this time.

A lymph node in the inguinal area was biopsied on the thirty-third day of life and a smear of the node revealed acid-fast organisms.

Because of a fall in the packed cell volume to 23 and a thrombocytopenia the patient was given 30 c.c. of whole fresh blood on the thirty-ninth day. Two days later the packed cell volume was 28, and the platelet count was 60,700 per cubic millimeter. The anemia has persisted but the platelet count rose slowly and has been adequate since the first 2 months.

The bone marrow and the inguinal lymph node grew acid-fast bacilli on Lowenstein-Jensen medium. The chloride and glucose concentrations in the spinal fluid were 116 mEq. per liter and 48 mg. per cent, respectively, and those of the blood obtained simultaneously were 97 mEq. per liter and 52 mg. per cent, respectively.

The infant has continued to receive Isoniazid 40 mg. per kilogram daily (orally after 11 days of intramuscular therapy). The streptomycin was decreased from 50 mg. per kilogram daily to 50 mg. per kilogram 3 times weekly on the seventy-fourth day of life. Vitamin and iron supplements were added to the diet at 6 weeks of age and solid foods were begun at the age of 4 months. The gain in weight has been slow as is shown graphically in Fig. 1.

The chest films taken at intervals and long bone and skull films have been interpreted by the radiologists as normal. Calcifications in the spleen and liver were first apparent on x-ray at the age of 4

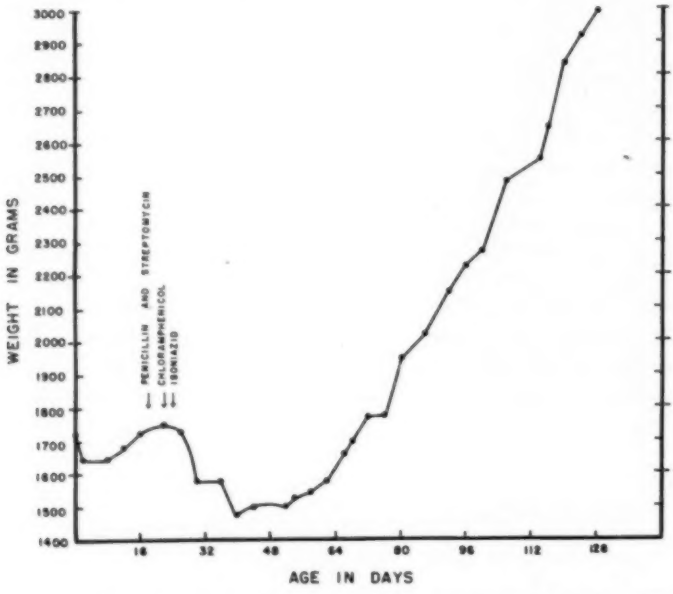

Fig. 1. The weight in grams is plotted against the age in days. Penicillin and chloramphenicol were discontinued at the time of initiation of Isoniazid therapy.

months. Chest films are shown in Fig. 2.

The first, intermediate, and second strength PPd's have remained negative.

The infant at the present time appears alert and vigorous. She has a large umbilical hernia but otherwise the physical examination is not remarkable.

DISCUSSION

In 1935 Beitzke[2] described the criteria which must be fulfilled before the diagnosis of congenital tuberculosis can be made, which is as follows.

1. The tuberculous nature of the lesion in the infant must be proved.

2. A primary complex in the fetal liver is proof of the congenital nature of the disease, since it can have arisen only from tubercle bacilli in the blood of the umbilical vein.

3. If there is no primary complex in the liver, the infection is congenital only (a) if tuberculous changes are found in the patient in utero, at birth, or within a few days after birth, and (b) in a child who lives longer than a few days if extrauterine infection can be excluded with certainty and if the child is immediately separated from the mother and kept in an environment free from tuberculosis.

Unfortunately, as has happened in a number of instances, the placenta was discarded and not examined. However, this patient fulfills the majority of the criteria put forward above, namely, (1) the tuberculous nature of the lesion was proved by demonstration of acid-fast bacilli on smear of the lymph node and by cultural growth of tubercle bacilli from the lymph node and bone marrow, (2) the child developed signs of illness on the eighth day of life and abnormal physical findings appeared on the twenty-second day, (3) the child was immediately separated from the mother after delivery, has had no further contact with her, and has remained in the Premature Nursery since birth.

The location of the primary complex in the liver cannot be ascertained with certainty but the paucity of pathologic changes on chest x-ray in addition to the later findings of calcification in the liver and spleen would suggest that the primary lesion was located in the liver.

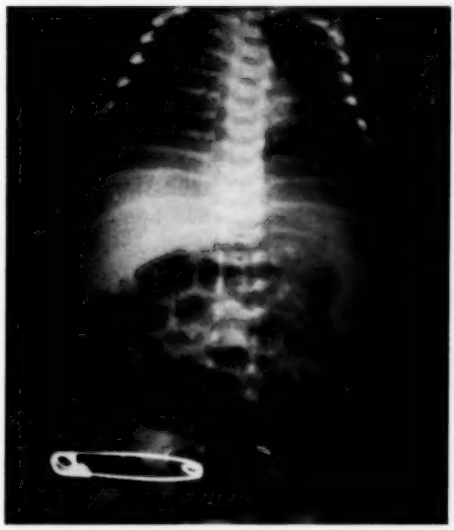

Fig. 2A. X-ray at 1 month of age. Splenomegaly is apparent.

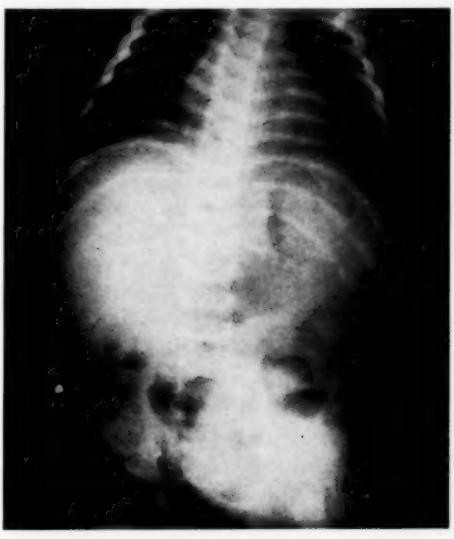

Fig. 2B. X-ray at 4 months of age. Calcification in the spleen is readily apparent. Some calcification can also be noted in the liver. The infant also has an umbilical hernia.

The generally accepted modes of transmission of tubercle bacilli to the fetus in utero are passage of tubercle bacilli from the placenta through the umbilical vein to the fetus and aspiration or ingestion of infected amniotic fluid. In the event that aspiration of infected amniotic fluid is the avenue by which infection occurs, the primary lesion is not in the liver but in the upper respiratory tract or lungs. Ingestion of infected amniotic fluid usually places the primary complex in the gastrointestinal tract and mesenteric lymph nodes.

The tuberculin skin test has remained negative which is in keeping with other reported cases. At the present time the relationship between cutaneous allergy and tuberculous disease is not clear and any reasons which might be put forth to explain the negative skin test would only be speculatory.

It is of interest to note that most of the cases that have been diagnosed as congenital tuberculosis have been in infants who were born prematurely. Of the ones that have survived, mental and motor retardation have been a conspicuous feature even though there was no direct involvement of the central nervous system by the tubercle bacillus.

At the present time this infant appears to be normal, but, of course, it is impossible to predict what the ultimate outcome will be until the child is old enough for her condition to be evaluated more completely.

SUMMARY

The total number of cases of congenital tuberculosis reported in the American and foreign literature has been determined. Another case which has thus far survived has been presented.

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Pheochromocytoma with secondary pyelonephritis

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ACCORDING to Cone and co-workers[1] 34 cases of pheochromocytomas in children less than 14 years of age have been reported. About 90 per cent of all pheochromocytomas reported have originated in the adrenal glands with 10 per cent of them being of extra-adrenal origin.[2]

In the case presented here, although the tumor was situated in an unusual site, an accurate diagnosis was made prior to operation. The patient seemed to have recovered completely, when observed more than 1 year after operation.

CASE REPORT

R. S. was a girl 9 years of age when she was admitted to hospital in August, 1958, for proteinuria. Several members of the family have exhibited allergic manifestations. As an infant she very often had upper respiratory tract infections and had bronchopneumonia on at least 2 occasions. Since 5 years of age she had suffered from bronchial asthma, and at 7 years she was hospitalized for it. Blood pressure then was normal.

For 2 to 3 months before the present admission to the hospital she had suffered from anorexia, loss of weight, nausea, headache, low back pains, and vomiting. During the week prior to admission she had spells of profuse sweating and suffered discomfort from heat without fever. There were no symptoms relative to the urinary tract and no edema. She was examined by her family physician and was found to have proteinuria and pyuria for which sulfa therapy was instituted. The pyuria disappeared, but the proteinuria persisted and she was admitted to the hospital.

At the time of admission the patient was rather thin. She weighed 2 kilograms less than she had 2 years earlier. She complained of weakness, but she did not seem to be seriously ill. There was no edema and the temperature was normal. There was resting tachycardia, with a pulse rate of about 140 per minute. The blood pressure was 155/105 mm. Hg. She had proteinuria, but no hematuria or granular casts. Blood urea was slightly elevated. Renal function tests were normal. The ocular fundi showed a decrease in the A-V ratio, but there were no A-V compression, no hemorrhages, and no exudates (hypertension Grade I).

The clinical findings suggested chronic nephritis but the history did not support it. The possibility of a hormone-producing chromaffin tumor was considered and urine

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Fig. 1. Intravenous pyelogram showing no excretion on the left side.

was sent for determination of catecholamines. In the meantime, intravenous urography revealed that there was no excretion on the left side (Fig. 1). A retrograde pyelogram showed a hydronephrosis and a distended ureter on the left side (Fig. 2). Roentgen examination of the adrenal glands by insufflation of oxygen presacrally did not reveal any abnormality. The possibility of a Goldblatt effect was considered. At this stage the results of the urinary catechol determination became available. The daily output of norepinephrine was 248 μg per 24 hours and of epinephrine 19 μg per 24 hours. A test with Regitine was positive. Palpation of the left side of the patient's abdomen was accompanied by a significant rise in the blood pressure. The patient undoubtedly had symptoms and signs of a hormone-producing chromaffin tumor, but it was just as certain that she also had a left-sided hydronephrosis. If all of the symptoms and signs were caused by a single lesion, one would have to assume that she had a hormone-producing chromaffin tumor situated between the middle and the lower third of the left ureter, which was also responsible for the hydronephrosis and pyelonephritis. On the basis of this assumption she was referred for operation 4 weeks after admission. The blood pressure was now markedly elevated with systolic pressures of 150 to 200 mm. and diastolic pressures of 110 to 150 mm. Hg. There was very marked hypertensive retinopathy (hypertension Grade IV).

The operation was performed under an anesthesia of nitrous oxide and ether. During the operation the patient received a slow intravenous infusion of a solution containing 2 mg. of norepinephrine in 250 c.c. of 5 per cent glucose, which was continued for another 48 hours. A left-sided oblique flank incision was made. As expected the left renal pelvis and the upper two-thirds of the ureter were dilated. Both adrenal glands appeared normal. Near the ends of the left common iliac artery and vein, where they were crossed by the corresponding ureter, a walnut-size tumor mass was found. The tumor compressed the ureter and the vessels at this site

Fig. 2. Retrograde pyelogram showing left-sided hydronephrosis and hydroureter.

and was fixed to the surrounding tissues. The upper part of the left ureter and the kidney had to be sacrificed together with the left common iliac vein. To dissect the tumor free from the common iliac artery it was necessary to divide it into two parts (Fig. 3). The dissection was difficult and considerable manipulation of the tumor was necessary. A representative part of the anesthesia chart (Fig. 4) shows the variations in the blood pressure related to manipulation of the tumor and the sudden fall in blood pressure when the tumor was removed. At this stage of the surgical procedure the patient was given 50 mg. of cortisone intramuscularly; the administration was continued in decreasing doses for a few days.

HISTOLOGIC DATA

The specimen consisted of the left kidney and 12 cm. of the proximal ureter. The lower end of the ureter entered a tumor mass measuring 4 by 2.5 by 2.5 cm. A second mass of similar tissue detached from the tumor measured 3.8 by 2.1 by 2 cm. (Fig. 3). The total weight of the tumor masses was 27 Gm. The cortex of the kidney was slightly reduced in width and the pelvis showed marked dilatation. The ureter was constricted by the tumor and moderately dilated above it (Fig. 5).

The tumor was lobulated, yellowish-grey in color, and, in the fresh state, gave a positive Vulpian reaction (greenish-blue color with iron chloride).

Microscopically the tumor consisted of elongated and polyhedral cells which gave a marked chromaffin reaction. Mitosis was rare. The nuclear staining showed little variation. The tumor was encapsulated and highly vascularized, but tumor tissue did not invade the vessels. In some of the arterioles of the tumor there was a hyaline sclerosis of the wall. Areas of hemorrhage and necrosis with leukocytic infiltration were seen in the tumor. No adrenal cortical tissue was seen (Fig. 6).

The tumor was adherent to the ureter. The muscle layer was atrophic and appeared infiltrated by the tumor, but the submucosa

Fig. 3. Photograph of tumor showing its relation to the left ureter and the common iliac artery and vein (marked by a pencil).

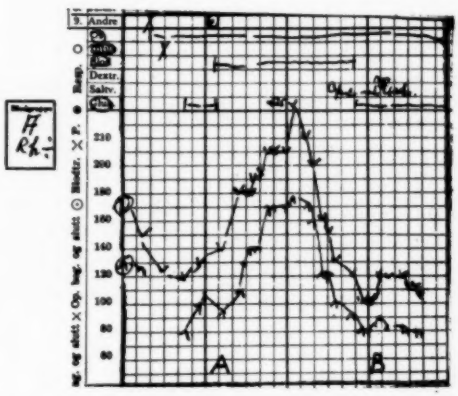

Fig. 4. Anesthesia chart showing blood pressure during operation. The left-hand numbers indicate blood pressure in millimeters of mercury. *A* indicates the point at which manipulation of the tumor commenced. *B* indicates point at which the tumor was removed.

Fig. 5. Gross specimen showing the relation of the tumor to the left ureter and explaining the pathogenesis of the hydroureter and hydronephrosis.

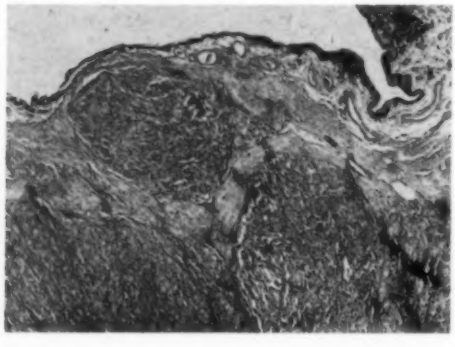

Fig. 6. Photomicrograph showing encapsulated and highly vascularized tumor. (× 35; reduced approximately ⅓.)

was not invaded. The ureteral wall contained clumps of lymphocytes. In the pelvis of the kidney there were some fibrosis and large areas of inflammatory infiltrations with numerous eosinophilic granulocytes and lymphocytes. In the kidney some tubules were dilated and tortuous; some contained hyaline casts and/or polymorphonuclear cells in the lumen. The glomeruli showed little change. In the parenchyma there was a diffuse infiltration of lymphocytes. Some groups of arterioles showed a slight but definite cellular hyperplasia of the muscle layer but no change in the elastic layer or any fibrosis. These arteriolar changes were not widely disseminated and were probably related to pyelonephritic scarring.

Chemical analysis of the tumor showed a concentration of 68 μg of epinephrine and 290 μg of norepinephrine per gram of tissue, amounts considered typical for a hormone-producing chromaffin tumor.

The pathologic diagnosis was a pheochromocytoma (paraganglioma) which was responsible for the hydroureter, hydronephrosis, and subacute pyelonephritis.

The postoperative course was uneventful. The observation time is now over 1 year and the patient has no clinical evidence of a pheochromocytoma. The blood pressure is normal with average values of 100/60 mg. Hg; the eye grounds are essentially normal, and the output of urinary catecholamines is normal.

COMMENT

Pheochromocytomă is an uncommon tumor in children but must be considered in patients with persistent or intermittent hypertension. Cone and co-workers reviewed the literature and found 34 reported cases of pheochromocytomas in children prior to 1956. Of the 46 tumors described, only 8 were situated outside the adrenal glands; the aortic bifurcation is the second most frequent site.

It was evident that our patient had a hormone-producing chromaffin tumor. There were also symptoms and signs of a left-sided hydronephrosis with pyelonephritis. It was logical to assume that the patient had a chromaffinoma located outside the adrenals which was responsible for the obstruction of the ureter. This was confirmed by operation,

supporting the aphorism of Robert Hutchison: "Do not diagnose two diseases simultaneously in the same patient."

It is of interest that the allergy, which did not bother her prior to the removal of the pheochromocytoma, has become troublesome since the tumor was removed and the concentration of catecholamines has returned to normal.

SUMMARY

A case of pheochromocytoma with secondary hydronephrosis and pyelonephritis in a 9-year-old child is presented. The tumor was removed. More than 1 year later the patient has no symptoms or signs of pheochromocytoma.

Professor O. Walaas, University of Oslo, performed the determination of catecholamines; Professor H. F. Gade, University of Bergen, performed the operation successfully; and Professor E. Waaler and Dr. P. Lexow, University of Bergen, carried out the histologic investigation. Their help and advice in the course of the study are deeply appreciated. Mr. T. Christensen, University of Bergen, gave technical assistance, for which I am grateful.

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Infantile cirrhosis of the liver (Sen's syndrome) with particular reference to the sulphur-containing amino acids

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IT WAS Sen[17] who first recognized as a distinct clinical entity the occurrence in young children in Calcutta of hepatomegaly associated with "slow fever, gradual emaciation, loss of appetite, slight jaundice, high-coloured urine," a tumid and shining abdomen, and a grossly enlarged liver which is hard, smooth, and nontender.

Since the discovery in 1887 of this disease which today is known as infantile cirrhosis of the liver, many theories as to its cause, including infectious, toxic, nutritional, hormonal, and genetic ones, have been suggested; none has been proved conclusively, either alone or in combination, to play a definite role in the causation of cirrhosis in children in India.

The disease has been referred to during its long history as biliary cirrhosis, intercellular hepatic cirrhosis, hypertrophic biliary cirrhosis of the liver, infantile cirrhosis of the liver, subacute toxic cirrhosis of the liver,[8] and more recently as Indian childhood cirrhosis.

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A summary of this paper was presented at the Ninth International Congress of Pediatrics in Montreal on July 22, 1959.

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Since the first description by Gibbons[5] in 1888 of the histopathologic changes in the liver which he described as a biliary or hypertrophic cirrhosis, numerous workers have studied the changes in sections of the liver. In 1935, Radhakrishna Rao[14] detected obliterative changes in the hepatic veins, but subsequent workers have failed to confirm this finding except for Jelliffe and associates[10] who found obliteration of the hepatic veins in a few of their cases. Detailed clinical and other data have been given by Chaudhuri[1] in a reported series of 76 cases of infantile cirrhosis of the liver.

Unfortunately, not much work has been carried out on Indian children with cirrhosis with respect to biochemical changes except for the traditional tests of hepatic function and with respect to a few constituents of blood, such as cholesterol and serum proteins, although the liver has been known for a long time to be an important site for protein and amino acid metabolism. As early as 1908 Jastrowitz[9] reported a greater urinary content of glycine in patients with hepatic damage as compared with that in normal patients. Attention was focused on the role of the sulphur-containing amino acids in liver disease, since Weichselbaum[20] in 1935

observed that a diet low in methionine and cystine causes damage to the liver irrespective of the presence or absence of choline. Detailed and painstaking experiments revealed basically two types of pathologic lesions in the liver: (a) necrosis and (b) fatty changes and cirrhosis. It was also shown that besides the sulphur-containing amino acids other nutrients either enhance or retard particular pathologic lesions of the liver.[16]

Metabolic studies on sulphur-containing amino acids have been reported in adults with cirrhosis.[4, 11, 19]

MATERIAL AND METHODS

The present study is concerned with the investigation of 5 children admitted to the Institute of Child Health, Calcutta, with advanced stages of infantile cirrhosis of the liver. Full histories were taken and complete physical examination with the following biochemical investigations were carried out on each child: electrophoresis of serum proteins, serum sodium and potassium, cholesterol, etc., according to the methods previously described by Chaudhuri and colleagues.[2] Electrophoresis of hemoglobin and fetal hemoglobin by the alkali denaturation method was done also. Special investigations, related to the study of amino acids in sera and urine of cirrhotic and normal children of the same age group with special reference to cystine and methionine, were done.

Histopathologic and histochemical methods. Histopathologic studies were done on liver tissue obtained by the punch biopsy method with the use of a Vim-Silverman needle. The approach to the liver was made approximately 1 inch lateral to the right border of the right rectus muscle immediately below the costal margin. The tissue was removed from the anterior surface of the liver, and varied in length from one-half to 1 inch. In one case, the needle biopsy was repeated after death. The procedure was carried out under local anesthesia, the patient having received 1 to 3 c.c. of paraldehyde intramuscularly ½ hour previous to the performance of the biopsy.

Routine hematoxylin and eosin staining

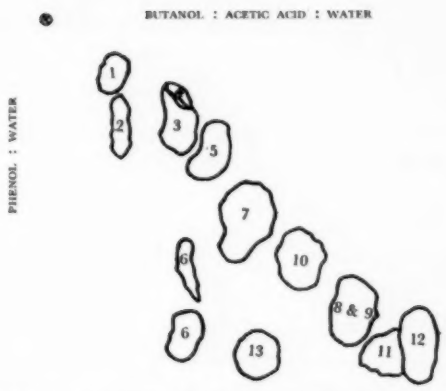

Fig. 1. Two-dimensional paper chromatogram of serum of a cirrhotic child (K. K.): 1, cystine; 2, basic amino acids; 3, glycine; 4, serine; 5, glutamic acid; 6, unidentified spots; 7, alanine; 8, valine; 9, methionine; 10, tyrosine; 11, phenylalanine; 12, leucine and isoleucine; and 13, proline.

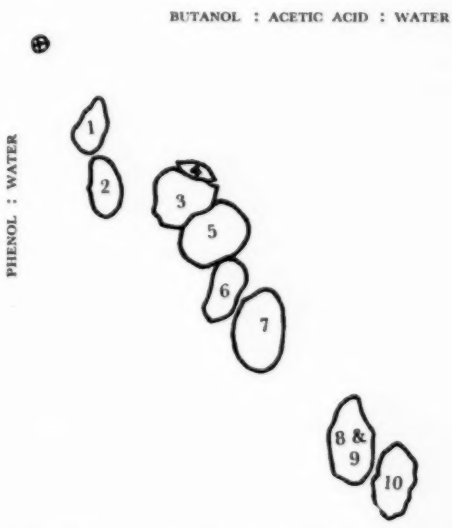

Fig. 2. Two-dimensional paper chromatogram of serum of a normal child (B. T.): 1, cystine; 2, basic amino acids; 3, glycine; 4, serine; 5, glutamic acid; 6, threonine; 7, alanine; 8, valine; 9, methionine; and 10, leucine and isoleucine.

of sections was done to confirm the diagnosis of cirrhosis. Sections were also stained to demonstrate changes in the fibrous tissue of the liver with the use of Mallory's and silver stains. In all 5 cases histochemical studies on

Table I. Pattern of amino acids in serum of cirrhotic and control infants

Name	*Interval between repeat analyses (days)*	*Phenyl alanine*	*Leucine and isoleucine*	*Methionine and valine*	*Tyrosine*	*Alanine*	*Threonine*	*Glutamic acid*	*Glycine*	*Serine*	*Cystine*	*Proline*	*Basic amino acids*
Cirrhotic group													
K. K.	—	++	++	++	Trace	++++	+	+	+++	+	+	+	+
	18	+++	+++	++++	++	++++	Nil	+++	++	+	+	+	+
L. B.	—	++	+++	++	+	++++	Nil	+++	+++	+	+	+	+
	17	++	++	++	++	+++	Nil	+	+	+	+	+	+
B. R.	—	++	++	+	+	++++	Nil	++	+	+	+	+	+
	26	+	+	+++	+	++++	Nil	++	++	+	+	+	+
G. S.	—	+++	+++	++	++	++++	Nil	+	++	+	+	+	+
	11	+++	+++	+	+	++++	Nil	++	+++	+	+	+	+
A. K. S.	—	++	+++	+	+	++++	Nil	++	++	+	+	+	+
	6	+	+		Nil	++++	Nil	++	++	+	+	+	+
Control group													
B. T.		Nil	++	++	Nil	++++	+	+++	+++	+	+	Nil	+
K. N.		Nil	+	+	Nil	++++	+	+++	+++	+	+	Nil	+
S. S.		Nil	Trace	++	Nil	++++	Nil	++	++	+	+	Nil	++
S. G.		Nil	+	+	Nil	++++	+	+++	+++	+	+	Nil	+

Table II. Pattern of amino acids in urine of cirrhotic and control infants

Name	*Interval between repeat analyses (days)*	*Phenyl alanine*	*Leucine and isoleucine*	*Methionine and valine*	*Tyrosine*	*Alanine*	*Threonine*	*Glutamic acid*	*Glycine*	*Serine*	*Cystine*	*Proline*	*Basic amino acids*
Cirrhotic group													
K. K.	—	Trace	Trace	++	++	++	++	+	+	+	+	Nil	+
	18	+	+	++	+	+++	++	++	++	+	+	Nil	+
L. B.	—	Nil	Trace	+	+	+++	+	++	++	+	++	Nil	+
	17	Trace	Trace	++	Nil	++	++	++	+++	+	+	Nil	+
B. R.	—	Nil	Trace	+++	++	++	++	+++	+++	+	+	Nil	+
G. S.	—	+	+	+++	Trace	++	++	++	++	+	Trace	Nil	+
	11	Trace	Trace	+++	Nil	++	+	++	++	+	+	Nil	+
A. K. S.	—	Trace	Trace	++	++	++	++	++	++	+	+	Nil	+
	6	Nil	Nil	++	?	++	?	?	+++	+	+	Nil	?
Control group													
B. T.		Nil	Nil	Nil	Nil	++	Nil	++	++	+	Nil	Nil	+
K. N.		Nil	Nil	Nil	+	++	Nil	+	++	+	Nil	Nil	+
S. S.		Nil	Nil	+	+	++	Nil	++	++	+	Nil	Nil	+
S. G.		Nil	Nil	Nil	+	++	Nil	++	++	+	Nil	Nil	+
B. S.		Nil	Trace	+	+	++	+	++	++	+	Nil	Nil	Nil

the biopsy material were done to determine the distribution of sulfhydryl groups (bound to protein) in the liver parenchyma. For these studies Bennett's reagent, 1-(4-chloromercuriphenylazo)—napthol-2, specific for sulfhydryl groups, was used for staining the sections of liver. The distribution of sulfhydryl groups and their relation to changes occurring in the plasma and urine have been studied.

There was difficulty in obtaining sections of normal liver for histochemical studies,

and the livers of 2 children who died from congenital hypoplastic kidneys and diarrhea, respectively, were studied, although it is realized that these do not represent normal children.

Biochemical investigations. Fasting samples of blood were taken in the morning from the femoral vein of each patient. The urine samples were collected, by catheter when necessary, under toluene. Since 24-hour collections were not possible in every case, it was decided to make the studies on fasting samples. The following investigations were done on the separated sera and urine samples.

1. *Amino nitrogen estimation: serum.* Amino nitrogen was estimated based on the principle of color development in the reaction between amino acids and β-naphthoquinone-4-sulphonic acid. The details of the method adopted were given by Danielson[3] and modified by Sahyhun.[15] The amount of serum taken for each estimation was 0.5 ml.

Urine. The amino nitrogen in urine samples was estimated by Sörensen's formal titration method.[7] The amount of urine taken for each estimation was 10 ml. The ammonia correction was not done.

2. *Amino acid studies in sera and urine: serum.* One milligram of serum was dried *in vacuo* in a small porcelain basin. The amino acids were extracted from the dried serum following the method of Gordon and Nardy.[6] The amino acid extract was finally dried *in vacuo* and 0.1 ml. distilled water was added to dissolve the hydrochlorides of the amino acids formed during the process of extraction. Twenty micro liters of the extract was spotted in one corner of a 20 cm. by 20 cm. Whatman No. 1 chromatography paper. Ascending two-dimensional paper chromatography was done for 7 hours in an all-glass chamber using phenol and water as the first solvent. The papers were dried by air and the chromatography continued for 16 hours with the use of butanol, acetic acid, and water as the second solvent. The papers were dried in an oven at 60° C. for half an hour and sprayed with 0.1 per cent Ninhydrin in water-saturated butanol. After color development for half an hour at 60° C., the amino acid spots were identified from prepared maps with the use of known amino acid solutions. The intensities of the colored spots were noted against each amino acid and arbitrarily compared (Figs. 1 and 2; Tables I and II).

Urine. Chromatography of the urine samples was carried out in the same solvent system used for serum extracts. As the urine samples streaked badly in the chromatograms, the following procedure was adopted for desalting the samples: 1 ml. of urine was dried *in vacuo* and the amino acids were extracted as the hydrochloride derivatives by several changes of small quantities of acetone and hydrochloric acid mixture (100 ml. acetone plus 1.6 ml. 6 N HCl). The extracts were dried and the final volume of 0.5 ml. was used for the urine of cirrhotic children and 0.25 ml. for that of normal children, since in the urine of the latter the concentration of amino acids was found to be less than in that of cirrhotic children (Table II; Figs. 3 and 4). Twenty-five micro liters of

Fig. 3. Two-dimensional paper chromatogram of urine of a cirrhotic child (K. K.): 1, cystine; 2, basic amino acids; 3, glycine; 4, serine; 5, glutamic acid; 6, threonine; 7, alanine; 8, valine; 9, methionine; 10, tyrosine; 11, phenylalanine; and 12, leucine and isoleucine.

urine extract was taken for each chromatogram. The solvents used were:

I.	Phenol	5 parts
	Water	2 parts
II.	n-Butanol	63 parts
	Glacial acetic acid (A. R.)	27 parts
	Distilled water	10 parts

Estimation of methionine and cystine in serum and urine. The buffered filter paper chromatographic method of McFarren and Mills[13] was employed for estimating methionine and cystine in the extracts of sera and urine prepared for two-dimensional chromatography studies. Strips of Whatmann No. 1 paper 22.5 cm. long and 2.5 cm. wide were taken for chromatography for methionine and cystine.

Descending chromatography was done in tall boxes lined with filter paper which dipped into the water-rich layer of the solvent. This ensured a more uniform vapor saturation essential for chromatography. For methionine, buffered m-cresol at pH 8.4 was used and buffered phenol at pH 1 was used for cystine. 0.5 ml. of m-cresol and 1 ml. of phenol were added to 50 ml. of the solvents for methionine and cystine, respectively. It helped to keep the solvent saturated with m-cresol or phenol during the test because of the small variations in temperature which occurred during chromatography. The chromatograms were developed with Ninhydrin as described by McFarren and Mills.

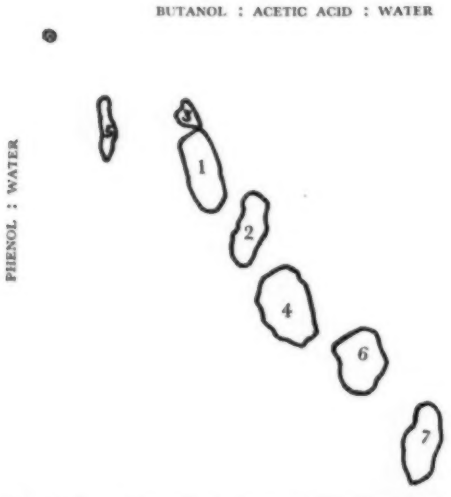

Fig. 4. Two-dimensional paper chromatogram of urine of a normal child (B. T.): 1, glycine; 2, glutamic acid; 3, serine; 4, alanine; 5, basic amino acid; 6, tyrosine; and 7, valine.

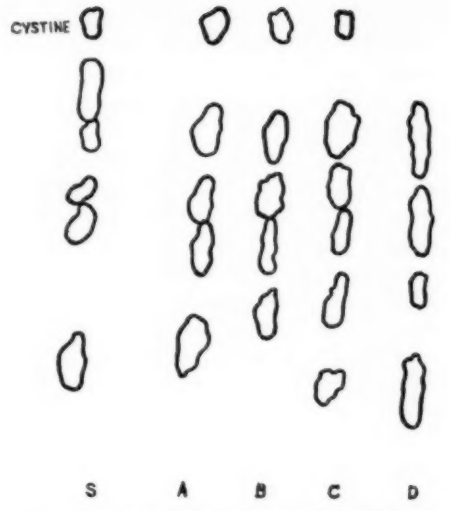

Fig. 5. Separated cystine spot in serum and urine of normal and cirrhotic children. Buffered filter paper chromatography with pH 1: *A*, serum of cirrhotic child; *B*, serum of normal child; *C*, urine of cirrhotic child; *D*, urine of normal child; and *S*, mixture of standard amino acids.

The separated methionine and cystine spots (Figs. 5 and 6 and Table III) were scanned in Lange's densitometer without any filter and the output of the photocell measured in a multiflex galvanometer with sensitivity at 1:10 and the shunt box setting at Gross 5, Fine 5 for methionine and Gross 3 and Fine 2 settings for cystine.

The maximum density of methionine and cystine spots were noted and the quantities in each sample were calculated from calibration curves prepared for methionine and cystine.

Calibration curves for methionine and cystine. A standard solution of 0.1 per cent solution of DL-methionine and 0.1 per cent of L-cystine in 0.1 N HCl were used.

The different quantities of the standard solution of DL-methionine were put on dif-

ferent strips with the help of the Agla micrometer syringe. The quantities in each strip varied from 1 to 12 μg. (1 to 12 μl); the average maximum densities from 1 μg. to 12 μg. were plotted to obtain the calibration curve (Table IV; Fig. 7).

The calibration curve for cystine was based on data obtained from densitometry performed on strips containing quantities of 1 to 10 μg. (Table IV; Fig. 8).

RESULTS

Clinical findings. The 5 children, 3 boys and 2 girls, ranged in age from 1½ to 3 years. The age of onset of the disease varied from 10 months to 2 years and 9 months, and the duration of the disease at the time of admission to the hospital varied from 2 to 8 months. Two children were first siblings, one the second sibling, one the fourth, and another the eleventh. Three were Bengalees, 2 Hindus and the other a Muslim; 1 was a Marwari and 2 were from other parts of India. Three of the families were nonvegetarian and 2 were vegetarian with milk in the diet. The Bengalee Muslim child came from a family of fish dealers who had ample supplies of fish and meat in the daily diet. There was a history of liver disease in other siblings of 2 patients, 1 of whom was the Bengalee Muslim whose first 2 siblings, maternal aunt, and maternal granduncle died from the same condition. Thus there was a history of the disease in 3 generations. All 5 children came from the middle and upper classes of society. One child, G. S., gave a history of fever with enlargement of the liver at 4 months of age, not associated with jaundice or anemia, which subsided shortly afterward. Another child had measles 1 year before the onset of cirrhosis. In all cases the onset of the disease could be described as insidious. All the children had been kept on a diet of either breast or cow's milk up to the age of 1 to 1½ years, with no attempt at weaning; only a small quantity of cereals such as rice or sago had been added well after the age of 1 year.

All the children showed a negative reaction to an injection of 1:100 dilution of Koch's old tuberculin and all were negative to Kahn and Venereal Disease Research Laboratory tests.

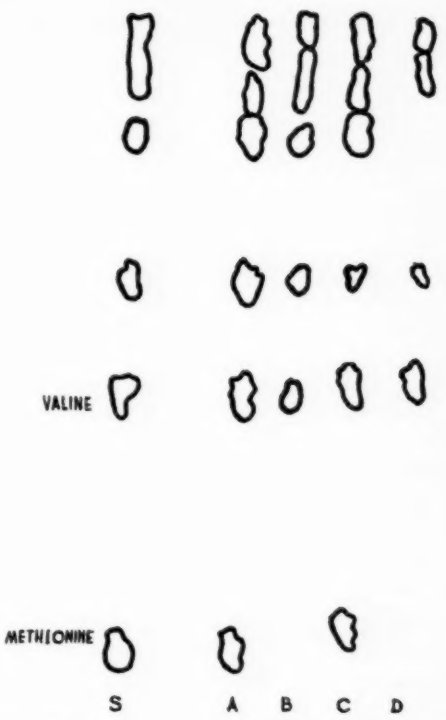

Fig. 6. Separated methionine spot in serum and urine of a cirrhotic child. Note methionine spot in serum and urine of a normal child. Buffered filter paper chromatography with m-cresol at pH 8.4: *A*, serum of cirrhotic child; B, serum of normal child; *C*, urine of cirrhotic child; *D*, urine of normal child, and *S*, mixture of standard amino acids.

The main symptoms were fever, abdominal distention, highly colored urine, and a change in the color of the stools. The presence of jaundice and edema was difficult to elicit since most parents failed to detect the slight yellowish discoloration of the eyes and puffiness of the feet. Table V summarizes the main features of the history and presenting symptoms.

Physical examination revealed irritability in all but 1 child, K. K., who was unusually quiet and cooperative for a child with cirrhosis. They all had a slight icteric tinge to the sclera. Hepatosplenomegaly was present

Table III. Amino nitrogen, methionine, and cystine in serum and urine

Name	*Interval between repeat analyses (days)*	*Serum*			*Urine*		
		Serum amino nitrogen (mg./100 ml.)	*Methionine content (mg./100 ml.)*	*Cystine content (mg./100 ml.)*	*Urine amino nitrogen (mg./100 ml.)*	*Methionine* content (mg./100 ml.)*	*Cystine* content (mg./100 ml.)*
Cirrhotic group							
K. K.	—	12.3	3.1	0.7	124.5	22.6	15.6
	18	6.0	1.6	1.1	68.6	7.5	16.0
L. B.	—	11.1	3.3	0.4	100.7	Nil	18.3
	17	10.4	1.9	0.4	33.6	Nil	14.7
B. R.	—	13.5	1.6	0.7	149.8	Nil	14.6
	26	19.5	2.6	0.7	—	Nil	—
G. S.	—	11.2	1.7	0.9	36.4	Nil	3.3
	11	10.8	Nil	0.8	29.4	Nil	3.3
A. S. K.	—	11.4	3.1	0.9	107.8	Nil	10.3
	6	11.3	Nil	1.0	79.7	Nil	11.6
Control Group							
B. T.		12.3	Nil	0.1	42.0	Nil	Nil
K. N.		11.2	Nil	Trace	97.1	Nil	Trace (inestimable)
S. S.		11.2	Nil	Trace	94.5	Nil	Nil
S. G.		11.8	Nil	Trace	130.6	Nil	Trace (inestimable)

*Estimations done on the fasting sample.

Table IV. Data for calibration curves for cystine and methionine

μg. of cystine	*Mean maximum density*	*Range*	*No. of strips scanned*	*μg. of methionine*	*Mean maximum density*	*Range*	*No. of strips scanned*
0.0	1.0	0.6 to 1.2	6	0	1.2	0.8 to 1.8	6
1.0	2.9	2.2 to 3.5	6	3	4.5	4.2 to 5.6	6
2.0	5.8	4.6 to 6.2	6	4	6.3	5.8 to 6.6	6
3.0	8.2	7.4 to 8.5	6	5	7.8	7.0 to 8.2	6
4.0	9.6	9.0 to 10.2	6	6	8.8	8.4 to 9.6	6
5.0	12.6	11.2 to 12.8	6	7	11.1	10.0 to 11.4	6
6.0	15.2	14.5 to 15.6	6	8	12.5	12.0 to 13.2	6
7.0	17.6	17.0 to 18.0	6	9	12.8	12.6 to 14.4	6
8.0	19.0	18.6 to 19.5	6	10	14.8	14.2 to 15.0	6
9.0	21.2	20.5 to 22.0	6	11	17.5	16.8 to 18.2	6
10.0	24.0	23.6 to 25.4	6	12	18.2	17.6 to 18.8	6

in all (Fig. 9) except A. S. K., who had only a grossly enlarged liver 5 fingerbreadths below the costal margin in the midclavicular line. All the children had temperature elevations of 99° to 103° or 104° F. Edema was present in 3 children, ascites in 1, and superficial abdominal veins were visible in 3. No child in this series had any hemorrhagic manifestations. Palmar erythema was seen in 2 cases. Table VI summarizes the main physical findings as seen in the 5 cirrhotic children.

Findings in the blood: All the children were anemic; hemoglobin ranged from 6 to 10.5 Gm. per cent, red blood cells from 2.4 to 3.9 million per cubic millimeter, white blood cells from 11,200 to 40,800 per cubic millimeter, and the erythrocyte sedimentation rate from 35 to 62 mm. per hour (Wintrobe). Bleeding and clotting times were within normal limits.

Histopathologic findings. Biopsy sections of the liver were studied in all 5 cases. Three patients (K. K., B. R., and L. B.) showed the characteristic changes associated with the disease, such as diffuse, patchy necrosis

of the liver cells (Fig. 10), with a moderate to severe degree of intercellular, intralobular, and interlobular fibrosis, round cell infiltration, especially around the portal areas, and pseudolobulation. In G. S. the liver cells had a vacuolated appearance, simulating glycogen storage disease of the liver. There were, however, fibrosis and pseudolobulation. The typical degenerative cellular changes were not seen (Figs. 11 and 12). The sections of A. S. K., on the other hand, showed wide-spread necrosis of the hepatic cells with diffuse fibrosis throughout (Fig. 13). Another peculiarity was the presence of a blue homogeneous material occupying large areas of the section prepared with Mallory's stain for reticulin. In these areas no liver cells or fibroblasts were seen. There was no attempt at pseudolobulation or regeneration of liver cells in these sections.

In none of these cases were obliterative changes seen in the central vein. It is, however, apparent that the 2 patients (G. S. and A. S. K.) behaved differently in many respects from the other 3 patients.

Biochemical findings. The values for bilirubin, icteric index, Van den Bergh's test, total cholesterol, serum sodium, and potassium are shown in Table VII. The analyses were repeated in most cases when a change was noted in the clinical condition. Except for A. S. K. and G. S., whose icteric index decreased, all other patients showed an increase in the bilirubin content and icteric index. There was a tendency toward hypocholesteremia as was reported in a previous paper by Chaudhuri and associates.[2] Sodium and potassium values were within the normal range as reported previously by Chaudhuri and colleagues.

Studies of serum protein. Table VIII shows the values for total serum proteins and their fractions. The total protein ranged from 5.0 to 8.7 Gm. per cent and, except for 2 patients (G. S. and A. S. K.), both of whom showed high albumin fractions and a normal gamma globulin fraction, the remaining 3 children gave values for the protein fractions very similar to the values found in a previous series reported by Chaudhuri,

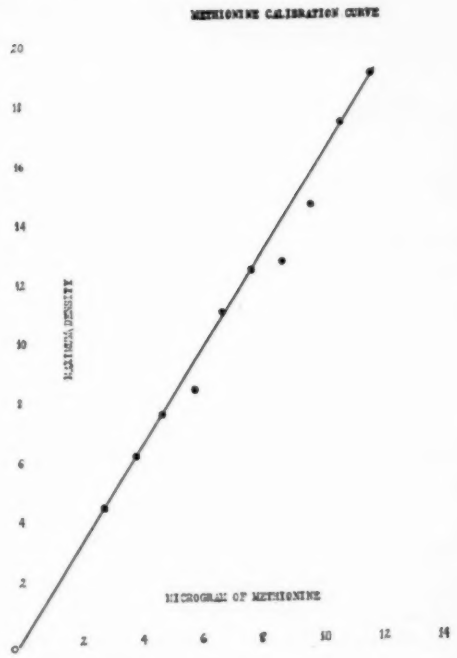

Fig. 7. Methionine calibration curve.

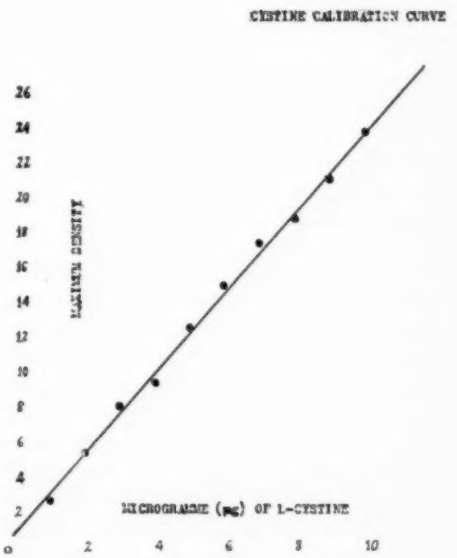

Fig. 8. Cystine calibration curve.

Table V. History and symptoms in infants with cirrhosis

Name	*Sex*	*Age (years)*	*Order of birth*	*Liver disease in siblings*	*Past illnesses*	*Feeding*	*Age at onset*
K. K.	M	3	First	Nil	Respiratory infections	Milk diet up to 1 year of age	10 months
L. B.	F	1½	Fourth	+	Nil	Milk diet up to 1 year of age	11 months
B. R.	F	1½	Second	Nil	Measles at 6 months	Milk up to present	10 months
G. S.	M	1½	Eleventh	+	Fever with hepatomegaly at 4 months of age; improved	Milk diet up to present with little rice	16 months
A. S. K.	M	1½	First	Nil	Nil	Milk diet up to 1 year of age	16 months

i.e., low albumin and high gamma globulin fractions. It may be noted here that the electrophoretograms of K. K., B. R., and L. B. revealed a wide-based gamma globulin fraction unlike those of G. S. and A. S. K. The presence of this wide base has been reported previously by Chaudhuri. It appears, however, that all cases of cirrhosis do not reveal this finding. The authors have separated the 5 patients investigated into two categories: (1) those showing the wide-based gamma globulin fraction and (2) those not showing this characteristic.

Studies of amino acids. Amino nitrogen values in serum and urine of cirrhotic patients ranged from 6.0 to 19.47 mg. per cent and 29.4 to 149.8 mg. per cent, respectively (Table III).

The two-dimensional paper chromatograms revealed that phenylalanine and tyrosine spots were absent in normal sera, whereas they were consistently dense (indicative of their concentration) in the sera of all the cirrhotic children, except in the repeat analyses of the serum of A. S. K. when tyrosine was not detected. Glycine and glutamic acid spots were more dense in the normal sera than in some of the serum samples of cirrhotic patients (Table I; Figs. 1 and 2).

Methionine and valine, the 2 amino acids which could not be separated by the solvent systems used, appeared denser in color when compared to those of the normal infants. In A. S. K. and G. S., however, methionine was not detected in the repeat samples by buffered filter paper chromatography, and therefore this dense spot in these 2 samples was entirely due to increased concentration of valine (Table I).

Another interesting finding was the presence of proline in the sera of cirrhotic children in sufficient concentration to produce a yellow spot after development with Ninhydrin. In normal sera, no proline was detected (Table I; Figs. 1 and 2).

Cystine was present in the urine of children with cirrhosis and in traces in the urine of normal children. Threonine was also present in the urine of all cirrhotic children except A. S. K's repeat sample but was absent in the urine of all normal children except 1 (Table II; Figs. 3 and 4).

The sulfhydryl groups in the liver biopsy specimens of cirrhotic patients stained uniformly poorly with Bennett's reagent, no selective area of the liver parenchyma showing enhanced staining for sulfhydryl groups. Unfortunately, no normal liver specimens were available for comparison but postmortem specimens taken from a patient with congenital hypoplastic kidneys and a patient

Appetite	Fever	Abdominal distention	Edema	Jaundice	Urine	Stool
Normal	1½ months	2½ months	?	Sclera 10 days	Highly colored 15 days	White
Poor	Continuous 11 months	?	Nil	Nil	Highly colored	
Anorexia 6 months	Low grade 6 months	6 months	Feet 15 days	Nil	Highly colored 5 months	Clay colored 2 months
Normal	Continuous 2 months	Gradual 2 months	—	—	Highly colored 2 months	Looseness and constipation
Anorexia 2 months	Intermittent 3 months	Gradual 2 months	—	Sclera	Highly colored 2 months	Clay colored 4 months

with diarrhea with fatty changes showed more intense staining of the liver parenchyma with Bennett's reagent as compared to those of the cirrhotic patients.

DISCUSSION

From the findings presented it is apparent that the 5 cirrhotic children investigated fall into 2 groups, namely, Group I consisting of K. K., L. B., and B. R., all showing a wide-based gamma globulin fraction in their electrophoretograms as well as hypergammaglobulinemia, and Group II consisting of G. S. and A. S. K. who had a normal gamma globulin fraction with no wide base. Other findings in Group II which differed from those of Group I included a fall in icteric index from 14.1 to 10.0 units in the case of G. S. and an increase in cholesterol from 66 to 100 mg. per cent after a period of 1 month. In addition, both children in Group II showed clinical improvement with respect to jaundice, edema, and general well-being during the period of hospitalization.

In A. S. K. (Group II) the albumin fraction, which was high initially, increased from 58.3 to 73.1 per cent after 6 days of hospitalization and the gamma globulin fraction fell from 17.0 to 9.9 per cent (within the normal range). Similarly with G. S., the other patient in Group II, the albumin fraction was initially higher (61.0 per cent) than is usually found in cirrhotic children, and there was no fall in the total protein or in the albumin fraction on repeat analyses.

Another important difference was the absence of a palpable spleen in A. S. K. (Group II), although the disease had already become far advanced and was associated with signs of portal hypertension. Usually in the well-established stage of the disease, cirrhotic children have hepatosplenomegaly. It is interesting to note in this connection, that Sen,[17] in his original description of the clinical findings in cirrhosis, referred to "a peculiar enlargement of the liver in young children, both male and female, without any enlargement of the spleen." Is it possible that Sen came across only this particular type of cirrhosis which A. S. K. represents, for it is inconceivable that an astute observer such as he could have failed to detect an enlarged spleen in a child.

Histopathologically, as mentioned previously, the children in Group II showed different changes from those seen in Group I. Furthermore, these 2 patients between themselves showed entirely different histopathologic changes as described above.

On the whole, it appears from the two-dimensional chromatograms that the ele-

vated amino acid levels in children with cirrhosis involve a relative increase of the essential amino acids as compared with the nonessential ones. It is unfortunate that the methods used did not give any clue to one of the essential amino acids of which lysine is most important during the period of growth and development. With respect to the presence of proline in serum, no quantitative studies were done on proline in this connection, but it would be of interest to study the behavior of this particular amino acid in greater detail in this condition since proline and hydroxyproline are important amino acids for synthesis of collagen tissues. It is hoped that more detailed study of the essential amino acids may provide clues as to the derangement of protein metabolism in this condition.

Fig. 9. Hepatosplenomegaly in B. R. (Group I) with second-stage cirrhosis.

The chromatographic patterns of the amino acids of urine in cirrhotic children also reveal some interesting findings. Cystine was present in all the samples in higher concentrations as compared with those of normal infants; the urine samples of normal children only showed traces on buffered filter paper chromatography.

It is interesting to note that though threonine was absent in the serum samples, it was present in the urine of all children with cirrhosis. It is difficult to explain this finding unless it is assumed that threonine may be one of the low-threshold amino acids. Threonine was absent in normal urine except in 1 case.

The studies of amino acid in cases of cirrhosis showed no significant differences in the amino nitrogen levels of sera when compared to those normal infants, though the amino acid patterns and levels of cystine and methionine investigated in these cases were different from those in normal children. Walshe[18] has mentioned that amino nitrogen levels may not show remarkable variation in children with cirrhosis unless the liver is damaged seriously. In K. K. the amino nitrogen level was about halved in the serum at the time of the repeat analyses, with a corresponding decrease in the methionine level, although the cystine level in the serum increased. The patient was in the terminal stage and died the same evening.

There was no quantitative relation between the levels of methionine and cystine in the serum, though it is well known that a close metabolic link exists between methionine and cystine (Table VII).

Cystine levels in the urine of the children with cirrhosis were increased several times when compared with the normal, which showed only traces. The cystine levels persisted at a high level on the repeat analyses. The cystine levels of urine in Group I patients were higher than in Group II. Excretion of methionine in the urine was high in only 1 of the cirrhotic patients. In others, methionine could not be estimated (Table III; Figs. 5 and 6).

Treatment. The elevated methionine and

Fig. 10. High-power photomicrograph of hepatic tissue showing necrosis of liver cells and presence of fibrosis in K. K. (Group I). (Hematoxylin and eosin ×450; reduced approximately ¼.)

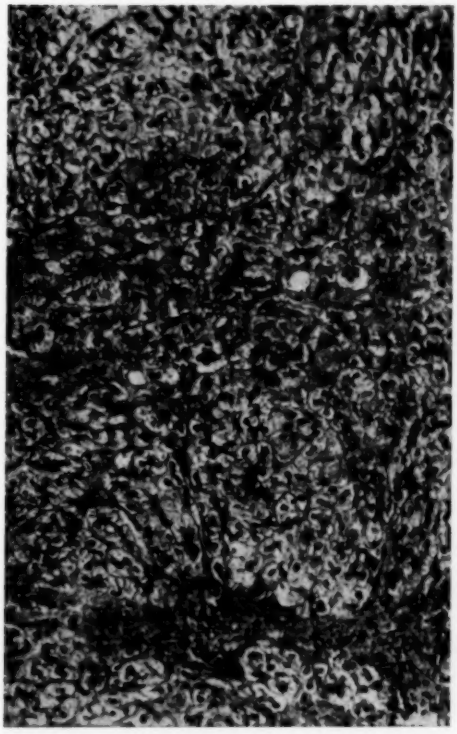

Fig. 11. Low-power photomicrograph of biopsy specimen from liver of G. S. (Group II). Note vacuolated appearance of the hepatic cells, simulating glycogen storage disease of the liver. The increase of fibrous tissue is evident in the section. (Hematoxylin and eosin ×150; reduced approximately ¼.)

cystine values in the sérum and urine of cirrhotic children suggest that therapeutic use of methionine and cystine in this condition may be of little value.

In the cases presented, prednisolone (15 to 20 mg. daily), chlorothiazide (0.5 Gm. daily), penicillin, Achromycin, neomycin, and a combination of streptomycin and Terramycin were administered when the other antibiotics failed to produce any response. Chlorothiazide (Chlotride tablets 0.5 Gm.) was of some help in reducing edema, but since the patients who received this drug were also on prednisolone, it is difficult to assess the effect of the former drug on edema associated with cirrhosis. Penicillin, Achromycin, and neomycin produced no appreciable effect on the temperature or on the general condition. A combination of streptomycin and Terramycin, as suggested by Krishna Rao,[12] has been tried but the results were disappointing.

SUMMARIES OF 5 INFANTS WITH CIRRHOSIS. GROUP I

Case 1. K. K., a 3-year-old boy, was admitted with a history of gradual enlargement of the abdomen for 2½ months, fever for 1½ months, yellow discoloration of the eyes and skin for 10 days, highly colored urine for 15 days, and whitish stools. He was the only child of a middle-class, vegetarian, Hindu family. There was a past history of respiratory infections and delay in

Fig. 12. High-power view of same section shown in Fig. 11. The large empty-looking cells and increase of fibrous tissue are seen. (Hematoxylin and eosin ×450; reduced approximately ¼.)

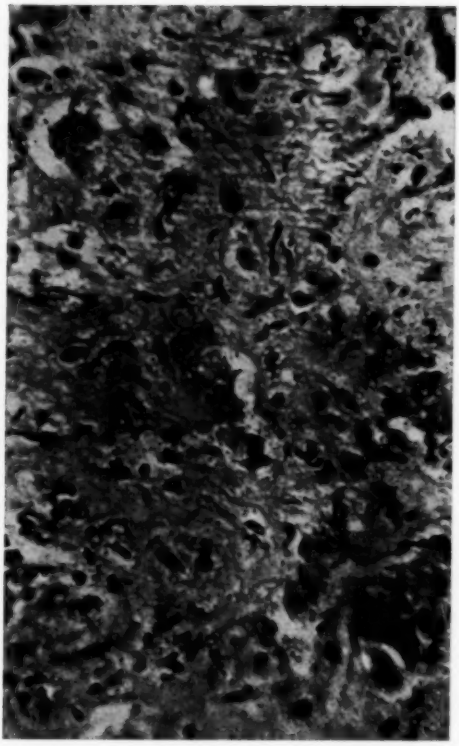

Fig. 13. Photomicrograph of hepatic tissue from A. S. K. (Group II) showing complete widespread destruction of liver cells. (Hematoxylin and eosin ×450; reduced approximately ¼.)

the milestones of development. The child was on breast milk supplemented by 16 ounces of cow's milk daily for his first year. A diet of mixed vegetables was started after this period. The disease was of 3 months' duration at the time of admission.

On examination the child was found to be unusually quiet and cooperative, which is unlike a cirrhotic patient, but he obviously was ill. The sclerae had an icteric tinge; there was edema of the feet and face as well as a moderate degree of ascites. The liver was enlarged, firm and smooth with a sharp edge, and palpable 4 fingerbreadths below the costal margin in the midclavicular line. A firm spleen was palpable 2 fingerbreadths below the costal margin and there was distention of the superficial abdominal veins. The child was running a temperature. A diagnosis of infantile cirrhosis of the liver was made. (Laboratory findings are given in Tables I to III and VII and VIII.)

Histopathologic examination of biopsy material from the liver revealed diffuse necrosis of the hepatic cells, distortion of the lobular architecture, fibrosis throughout the parenchyma, and infiltration of round cells.

Progress. Within 20 days of admission the jaundice and ascites had increased; bilirubin rose to 10.2 mg. per cent, icteric index to 82.2 units, potassium increased to 6.0 mEq. per liter, and sodium dropped to 126.0 mEq per liter. Following open operation for removal of hepatic tissue for histopathologic examination, ascitic fluid continued to drain through the incision and there was some de-

Table VI. Physical findings in infants with cirrhosis

Name	General condition	Edema	Jaundice	Ascites	Liver	Spleen	Superficial abdominal veins	Hemorrhage	Temperature
K. K.	Quiet, cooperative, palmar erythema	+ Pitting	+ Sclera	+	++++	++	+	–	+
L. B.	Irritable	+ Pitting	+ Sclera	?	+++	+	–	–	+
B. R.	Irritable, moderately well nourished, palmar erythema	–	+ Sclera	–	++++	++	–	–	+
G. S.	Irritable, anemic	–	+ Sclera	–	+++ (Granular)	++	+	–	+
A. S. K.	Irritable, anemic	+	+ Sclera	–	+++++	–	+	–	+

Table VII. Changes in certain constituents of serum at different intervals

Name	Interval between repeat analyses (days)	Bilirubin (mg.%)	Icterus index (units)	Cholesterol (mg.%)	Sodium (mEq./L.)	Potassium (mEq./L.)
K. K.	—	1.9	6.0	118	135.0	4.3
	18	10.2 (10 days later)	16.0	–	126.0	6.0
L. B.	—	—	7.0	114	147.0	4.5
	17	3.2	7.0	154	137.0	4.5
B. R.	—	2.3	5.0	90	140.0	4.8
	26	7.3	9.0	128	135.0	4.3
G. S.	—	1.1	3.0	63	154.0	4.4
	11	1.0	3.0	66	137.0	5.6
	30	1.0	2.0	100	139.0	4.5
A. S. K.	—	8.3	14.0	124	132.0	5.0
	6	9.1 (21 days later)	10.0 (9 days later) 68.0 (12 days later)	158	132.0	3.6

lay in healing. Edema then decreased and the child became emaciated and died from cholemia after 20 days of hospitalization. Repeat examination of postmortem hepatic tissue removed by biopsy revealed large multinucleated liver cells and fibrosis.

Case 2. L. B., a 1½-year-old Bengali Muslim girl, was admitted with a history of continuous fever for 11 months, abdominal distention for 3 months, and highly colored urine and diarrhea with an occasional whitish stool. The child was the fourth and last sibling of a nonvegetarian family engaged in the fishing business. Two other siblings (first and second), the maternal aunt, and granduncle also died from infantile cirrhosis.

Table VIII. Total serum proteins and their fractions in infants with cirrhosis and control infants

Name	*Interval between repeat analyses (days)*	*Total protein (Gm. per cent)*	*Albumin (%)*	*Globulins per cent*			
				Alpha₁	*Alpha₂*	*Beta*	*Gamma*
Cirrhotic group							
K. K.	—	8.7	33.5 (2.8 Gm.)	6.7	10.0	3.3	46.5 (wide-based)
	18	5.3	46.2 (2.4 Gm.)	1.7	9.8	1.7	40.6 (wide-based)
L. B.	—	7.5	52.3 (3.9 Gm.)	2.2	5.9	9.5	30.1 (wide-based)
	17	6.3	44.4 (2.7 Gm.)	1.6	5.2	3.5	45.3 (wide-based)
B. R.	—	5.0	48.0 (2.4 Gm.)	2.8	8.4	6.4	34.4 (wide-based)
	26	5.6	43.2 (2.4 Gm.)	2.7	3.6	4.5	46.0 (wide-based)
G. S.	—	6.8	61.0 (4.1 Gm.)	3.8	8.5	10.1	16.6
	11	6.8	61.8 (4.1 Gm.)	0.8	12.7	10.5	14.2
A. S. K.	—	5.8	58.3 (2.8 Gm.)	3.8	9.0	11.9	17.0
	6	5.0	73.1 (3.6 Gm.)	0	6.3	10.7	9.9
Control group							
B. T.		5.0	62.3 (3.1 Gm.)	1.6	11.5	13.1	11.5
K. N.		6.2	65.3 (4.0 Gm.)	0.8	7.3	14.0	12.6
S. S.		6.5	63.2 (4.1 Gm.)	2.7	11.5	12.4	10.2
S. G.		5.8	68.9 (4.0 Gm.)	1.9	9.9	10.4	8.9

The infant was kept on a milk diet up to 1 year of age after which rice was started.

On physical examination she was irritable with an icteric tinge to the sclerae, pitting edema of the feet, an enlarged, smooth, and hard liver with a sharp edge palpable 3 fingerbreadths below the costal margin in the midclavicular line, and a spleen which was just palpable. (Laboratory findings are shown in Tables I to III and VII and VIII.)

Biopsy section of the liver showed changes typical of cirrhosis. There was diffuse necrosis of cells with pseudolobulation and a moderate degree of fibrosis.

Progress. Two weeks later the child showed slight improvement and pitting edema decreased. Icteric index was 36.0 units and cholesterol 154 mg. per cent.

Case 3. B. R., a 1½-year-old Bengali Hindu girl, was admitted with a history of anorexia, low-grade fever, and abdominal distention for 6 months, swelling of the feet for 15 days, highly colored urine for 5 months, and intermittent clay-colored stools for 2 months. The child was the second of 2 siblings belonging to a middle-class nonvegetarian family. She had measles at 6 months of age and was otherwise quite normal until the age of 10 months when the present illness started. She was breast fed for 1 month,

then placed on Lactogen for 6 months followed by cow's milk. No attempt at weaning was made. At the time of admission the disease was already of 8 months' duration.

On physical examination she was well nourished and irritable, with a slight icteric tinge to the sclera and no detectable edema or ascites, a grossly enlarged, nontender liver 4½ fingerbreadths below the costal margin which was firm and smooth with a sharp margin, and a firm spleen palpable 2½ fingerbreadths below the costal arch. There was well-marked palmar erythema. A provisional diagnosis of infantile cirrhosis of the liver was made. (Laboratory findings are given in Tables I to III and VII and VIII.)

Biopsy specimen of the liver showed characteristic changes of cirrhosis, most cells showing degeneration. Some attempt at pseudolobulation was seen. There was a moderate degree of fibrosis.

Progress. Temperature returned to normal on Achromycin drops 7 minims 3 times a day. Edema decreased after administration of prednisolone 10 mg. daily and chlorothiazide tablet 0.5 Gm. daily, but jaundice became more intense. Bilirubin rose to 7.3 mg. per cent, and icteric index to 44.9 units, but after stoppage of the drugs the fever and edema returned and the condition deteriorated. The child was discharged to be followed up in the Outpatient Department.

GROUP II

Case 4. G. S., a 1½-year-old Marwari Hindu boy, was admitted with a history of continuous fever for 2 months, gradual enlargement of the abdomen for 2 months, highly colored urine for 2 months, and loose stools alternating with constipation for some time. The appetite was normal. The patient was the eleventh and last child of vegetarian parents belonging to the upper class. There was a history of liver disease with recovery in the ninth sibling. This patient gave a history of fever with hepatic enlargement at the age of 4 months, not associated with jaundice or anorexia. He recovered and remained well until the onset of the present condition. He was breast fed up to the time of admission and this diet was supplemented with 24 ounces of cow's milk daily and a little rice.

On physical examination he was anemic and irritable, with jaundice of the sclerae, a liver enlarged to 3½ fingerbreadths below the costal margin in the midclavicular line which was nontender, firm in consistency, with a slightly granular surface and a sharp edge, a firm spleen enlarged to 2 fingerbreadths below the costal margin, and prominence of superficial abdominal veins. There was no edema or ascites. (Laboratory findings are given in Tables I to III and VII and VIII.)

Histopathologic examination revealed large empty-looking liver cells containing centrally placed nuclei with the cell membrane intact, resembling glycogen storage disease of the liver. Fibrous tissue was fairly abundant between the cells and lobules. Round cell infiltration and pseudolobulation were present, but necrosis of the cells as seen in other cases was not present.

Progress. The child was put on prednisolone 15 mg. daily, zinc oxide powder, and penicillin and showed clinical improvement within 14 days. The icteric tinge disappeared and the liver felt somewhat softer but was larger. Two weeks subsequent to this, however, the child deteriorated; the liver was found at the level of the umbilicus and was hard and smooth with a sharp edge; the spleen was 3 fingerbreadths enlarged. There was nonpitting edema of the feet but no jaundice; bilirubin was 1.0 mg. per cent, icteric index 10 units, and cholesterol 100 mg. per cent. The child was placed on intramuscular streptomycin ¼ Gm. daily and Terramycin 5 minims 3 times a day (100 mg. daily). When seen last 1 week later, the child was pale with slightly puffy eyelids but no edema of the legs. The liver and spleen showed no change. The urine was straw colored but the stools were pale.

Case 5. A. S. K., a 1½-year-old Hindu boy, was admitted with a history of passage of clay-colored stools for 4 months, intermittent fever for 3 months, anorexia for 2 months, highly colored urine for 2

months, gradual enlargement of the abdomen for 2 months, and yellowish discoloration of the eyes for 1 month. This patient was the only child of nonvegetarian upper middle-class parents. There was no history of any previous illness. He was breast fed up to 1 year of age. In addition he received 12 ounces of cow's milk with Lactogen and sago daily. On examination the child was found to be anemic and irritable. The sclerae were mildly jaundiced; there was nonpitting edema of the feet; the liver was grossly enlarged, firm, smooth, and with a sharp edge 5 palpable fingerbreadths below the costal margin in the midclavicular line. The spleen could not be felt and there were prominent superficial veins over the abdomen. (Laboratory findings are given in Tables I to III and VII and VIII.)

Histopathologic examination revealed widespread necrosis of the hepatic cells, with complete disruption of the lobular architecture. There was no attempt at regeneration and pseudolobulation was not seen. Mallory's reticulin stain showed diffuse fibrosis.

Progress. Edema increased during hospitalization and prednisolone 15 mg. and chlorothiazide 0.5 Gm. (Chlotride tablet) daily were started. On this therapy edema decreased within 1 week and the weight dropped from 10.0 to 8.7 kilograms. Jaundice had decreased prior to the administration of Chlotride and the icteric index had fallen from 70.0 to 51.0 units. After 4 days of Chlotride therapy jaundice started to increase and following the stoppage of Chlotride edema increased again. When last seen 5 weeks after admission, the general condition was deteriorating, jaundice was intense and generalized, and there was tense ascites. The child was started on intramuscular streptomycin and Terramycin 600 mg. daily.

CONCLUSIONS

The authors suggest that infantile cirrhosis of the liver, though apparently a clinical entity, should not be considered a disease entity, and that probably several types of cirrhosis occur within the age range of 6 to 18 months when the cirrhotic condition usually manifests itself. It may be necessary to carry out more detailed and comprehensive biochemical and histochemical investigations in order to distinguish between the types that may occur.

Therefore, the authors prefer to use the term "syndrome" with reference to the condition. In order to identify the syndrome it is suggested that it be called after the man who discovered it so many years ago—hence Sen's syndrome.

The poor staining for sulfhydryl groups in the livers of cirrhotic children probably indicates reduced synthesis of sulfhydryl group containing proteins of the liver. However, quantitative estimations of the sulfhydryl groups bound to the proteins in the liver were not carried out. It is known that methionine, as well as cysteine, are the important sources of sulfhydryl groups for synthesis of the sulfhydryl group containing proteins. Raised serum concentration of methionine and the lowered level of sulfhydryl groups in the liver possibly suggest a disturbance of synthesis of the sulfhydryl group containing proteins of the liver.

SUMMARY

The paper presents the findings in 5 cirrhotic children with respect to clinical, histopathologic and biochemical investigations. The cases studied could be separated into 2 groups: Group I having a wide-based gamma globulin fraction in the electrophoretogram associated with hypergammaglobulinemia; and Group II having a normal gamma globulin fraction.

The suggestion is put forward that the condition is not a disease entity but a syndrome. Thus it is suggested that it be called Sen's syndrome after the Calcutta clinician who discovered the condition.

Clinically, biochemically, and histopathologically, Group I patients have shown certain differences from Group II.

Cystine levels in the urine of children with cirrhosis were much higher than in the urine of normal children and urinary cystine in Group I cases was higher than in those of Group II.

Phenylalanine and tyrosine, though absent in normal sera, were found in high concentrations in the sera of cirrhotic children but not in those of the normal children.

Proline was present in the sera of all cirrhotic children but was absent in the sera of normal children. Apparently the elevated amino acid level in cirrhotic children results from a relative increase of the essential rather than of the nonessential amino acids.

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TROPICAL PEDIATRICS

Indigenous medical systems and child health

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FOR PEDIATRICIANS working in the tropics outside their own culture the importance of understanding indigenous medical beliefs, whether systematized or not, cannot be overestimated. Probably more than half the ill children in the world today are receiving treatment based on local concepts which differ widely from those of the Western world but which have been accepted, valued, and understood by generations of parents in other regions. Evidence for this in Africa alone is only too obvious to all who have ever examined large numbers of African children; it is rare to find no amulets or scars of medicinal incisions (Figs. 1 and 2).

Indigenous medical systems offer a two-sided challenge to the scientific pediatrician: deleterious opposition and influences to be judiciously overcome and beneficial principles, behavior, and methods to be studied and accepted. Both are of significance because at present less technically advanced communities have more to gain from science and, at the same time, scientific pediatrics is now better equipped to gain from traditional medicine than ever before.

For the scientifically trained pediatrician to be successful in a foreign cultural milieu he must be prepared to learn as much as possible about local medical beliefs[1] which should, as Foster says,[2] include attitudes and practices associated with health, the prevention of disease, ideas as to cause of disease, and methods of cure—in the broadest sense, folk medicine.

ETIOLOGY OF DISEASE

Among peoples whose "world view" is non-scientific and who are often illiterate, disease is frequently thought to fall into one of two categories:

(1) magical-supernatural and (2) physical-empirical.

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Magical-supernatural. This group will include diseases believed to be due to such occult agencies as sorcery[3] (Fig. 3), black magic, curses, witchcraft (especially by a foreign tribe),[4] the evil eye, wrath of the gods, the influence of ghosts, evil spirits (such as the *loups-garoux* or werewolves of Haiti),[5] ancestral shades,[6, 7] unfavorable stars, "soul loss" (Cuna Indians, Panama),[8] or even to the effect of rainbows (as in the Sebei of Uganda)[9] or as a result of infringement of the rules (especially the sexual conduct of a child's parents) or breach of taboo (such as, for example, eating a clan totem in some African groups).

The belief in a dual supernatural-natural etiology is common. For example, snakebite of a child may be considered to have two causes: the "apparent" being the actual snake venom and the "real," being some form of malevolent witchcraft which caused the snake to attack the particular child.*

The apparent effectiveness of witchcraft is due largely to coincidence, at least in young children for whom in the tropical peasant environment a procession of disease is only too usual; in adolescents and adults effects are usually psychosomatic as a result of anxiety when a person becomes aware that someone is trying to bewitch him. This "malignant anxiety," together with dehydration, inanition, and secondary infection, can result in death in extreme cases.

Among the so-called bewitchment syndromes, the concept of the evil eye (*mal de ojo, maladie de diable, maljok, nazar,* "overlooking") has a wide distribution, including many rural parts of Latin America, the Caribbean islands, tropical Africa, and southeast Asia. Broadly, the belief is that some persons, in particular barren women, have the power, either maliciously or unwittingly, of casting the evil eye and causing illness, especially in handsome infants. The same effect is sometimes thought to be produced by the praising of a child; thus, in parts of the Sudan, for example, a mother must never be complimented on her baby without a preliminary deflectory *ma'ashallah* (through the grace of God). Perhaps, in a similar way, some Baganda in rural areas believe that counting their children is to invite illness and death among them, giving rise to obvious difficulties in collecting demographic and statistical information.

Although a belief in sorcery in some communities may be an important sanction against social misbehavior within the group, it also has many definite and immediate influences in the field of public health as, for example, in many of these practices, the

Fig. 1. African infant with multiple charms (Yambio, Southern Sudan).

*One of the authors (F. J. B.) was once called to a Zulu hut for a child who had a large thorn deep in her foot, together with extensive suppuration. Shortly after removing this foreign body and administering antibiotics and dressings, one of the most influential female diviners, who had also been summoned, appeared. It was mentioned that the patient had already been successfully treated; however, the diviner explained that she had been called to make the "real" diagnosis, that is, who had bewitched the patient so that she had been so foolish as to step on a thorn.

Fig. 2. Mukiga African infant with medicinal branding scars on abdomen (Kigezi, Uganda).

magicians or witches are thought to need a portion of the victim's body, clothing, or food in order to cast a spell. Because of this great care may have to be taken with the disposal of exuviae (hair and nails) and, in some parts of the world, feces will have to be buried secretly in a secluded spot. For the same reasons, there are frequently difficulties in taking blood samples or of removing biopsies, either surgically or at autopsy.

Failure to concede an infectious agent as a possible cause can result in unchecked spread of conditions such as tuberculosis or venereal disease. The Zulu, for example, believe tuberculosis to be due to poisoning by an ill-wisher and that the only really effective treatment is from an indigenous practitioner. Delay in seeking correct treatment or in persisting with it is, therefore, the rule and the idea of infectivity of sputum can hardly be entertained.

Similarly, a program to diminish mortality rates can seldom be understood in rural Africa as deaths are rarely attributed to preventable causes, as understood by the scientific pediatrician. Falsely sworn oaths by a father are one of the recognized causes of child deaths in Kikuyu and Embu society. In some groups there is the idea of death being justice, so that maternal death in childbirth may be considered a punishment for women having been unfaithful.

Belief in bewitchment as a cause of the death of a child can lead to much trouble in a family as motives are always sought. Jealousy and plans for inheritance are easily read into such an occurrence in a polygamous home. This often explains the bitter tensions among co-wives which in turn disrupts the harmony which should characterize the child's early family life.

Motivation for following hygienic health practices is often lacking if witchcraft is considered etiologic and many public health programs have failed from lack of understanding of this point. Laws to enforce the construction of pit latrines, to diminish gastrointestinal infections and infestations in children in tropical Africa have failed without very careful preparatory health education programs to first modify conceptions of etiology. If one believes that putting a child's feces in a recognized spot will enable an ill-wisher to come at night to obtain some for bewitchment purposes, it is unlikely that the argument about giving hookworm to someone else will prevail. On the other hand, is it ethical to tell people that a latrine is the one place that can be locked so that no feces can be stolen for bewitchment purposes, a very effective argument for getting people to build latrines in Zululand?

Physical-empirical. According to Foster[10] diseases in which the cause is often wrong according to the scientific observer with his fuller knowledge, but not according to the more limited framework of local beliefs, can be classified in this group. Thus leprosy may be thought to be due to eating pork, a-

among the Azande of the Southern Sudan, or malaria due to the consumption of green coconuts as was thought some years back in rural West Bengal. Also, disease may be linked with the weather or with climatic conditions in the same way as the phrase "to catch cold" is used in English; for example, *mal aire* in Latin America and *tonda* in parts of India (cold weather) are considered to be responsible for disease.

Sometimes these empirical beliefs are built on an apparently unscientific, but systematized, theoretic basis related to different concepts of body structure and physiology. Of these, an excellent example is the "hot-cold" (*caliente-frio*) theory of disease widely prevalent in South America. This may stem ultimately from the humoral pathology of Hippocrates and Galen, which may possibly have reached medieval Europe via the Arab world and was then transmitted to Hispanic America by the conquistadors, so that selected aspects of this theory, particularly the concept of heat and cold as qualities of the body, of types of illness, and of foods and herbs has become a part of present-day folk belief.[1] In this context it is of interest to note that a similar hot-cold (*garam-tonda*) concept is prevalent in India and Pakistan.[11] As this seems to be an ancient belief mentioned in early Sanskrit literature, it seems possible that it, together with the *Tridosha* theory of *Ayurveda,* may have spread from India originally and influenced and molded early Greek thought in this respect. According to this prescientific theory of physiology, the body is made up of 3 fundamental principles or humors (*doshas*) and, if the balance between them is upset, various diseases with certain clinical features result. In addition, certain foods, medicines, and even habits may aggravate one or other of these vital principles.

Similarly, the Batonga of Nyasaland have the view that a state of near-diarrhea is the norm for adults and children, so that less than several bowel motions daily is considered as abnormal.[12] Disease may by some peoples be related to, or enter the body via, the anterior fontanelle[7] (which can be paralleled by the seventeenth century English diagnosis of "mould fallen"), or to a displaced xiphisternum. Finally, some illnesses may be thought to be inherited within clans or families, as with tuberculosis among the Baganda, so that concealment may occur to avoid stigmatizing a family.

Poison is often suspected of playing a part in the cause of disease, both in a physical sense and also in a semimagical way, as when someone walks on poison scattered in his path by a sorcerer.

Closely associated with the group's ideas concerning disease causation must inevitably be linked their attitudes toward health, illness, and death. For example, disease and death may be accepted fatalistically as part of an ordained pattern or fate (as with the *Karma* concept in Hindu philosophy).

Special diseases in children. Most peoples recognize the vulnerability of children to disease and take special precautions based on local ideas of etiology. Various serious syndromes in young children are often known and given specific names, such as febrile con-

Fig. 3. Advanced Kuru in older child, showing extensive paralysis, loss of speech, and decubitus ulcer. This disease is locally regarded as the result of sorcery (Fore, New Guinea).

vulsions (*ennyonyi*) and *obwosi* (kwashiorkor) among the Baganda.

With regard to kwashiorkor, indigenous ideas of malnutrition as an etiologic factor appear to be unusual. The Zulu regard gingering hair as a normal process of infant maturation, while many groups make a correct sociologic diagnosis; both the words kwashiorkor in Ga and *obwosi* in Luganda refer to a child "displaced" by another pregnancy.

It is always instructive to study diagnoses made in a community as it gives some idea as to what extent diseases are differentiated. Among the Zulu some infectious fevers are specifically identified, including influenza, the common cold, and such childhood infections as measles, chicken pox, and whooping cough. Gastroenteritis, kwashiorkor, and congenital syphilis are ascribed either to an unhealed umbilicus, a placenta that has appeared flat instead of folded, or to the pregnant mother having walked over a place struck by lightning.

Congenital anomalies, as remarked by Warkany,[13] have been noted from time immemorial, and are often thought to be due to maternal sin or to the impression of something seen by the mother, such as a monkey, or eaten by her, such as catfish, affecting the appearance of the child. Attitudes toward different congenital abnormalities, as with other unusual events, such as twins and being born with teeth or with the upper incisors erupting first, vary, but often they are regarded as stigma of good luck or the opposite.

Classification of disease. Apart from concepts of etiology, diseases are often considered in 3 groups: (1) trivial or everyday, (2) "European," that is responding to Western therapy, including yaws and malaria, and (3) African (or whatever the local group may be) and not likely to be either understood or treated successfully by scientific medicine, including, therefore, "bewitchment syndromes" presenting as psychosomatic illness.

As Tanner noted among the Sukuma of Tanganyika, diseases are often named: (1) after symptoms (i.e., diarrhea), (2) after something the disease resembles (i.e., *buludoke* for jaundice, from the word for banana), (3) after the affected part (i.e., spleen), and (4) after the alleged cause (i.e., *mako ga busangila* for emaciation in childhood, meaning "defilement of mixing" or adultery).[14]

MEDICAL PRACTITIONERS

Nonscientific medical practitioners in different parts of the world vary from those with an ancient codified system, such as used by the Ayurvedic physicians of India, to the village geomancer with his stock of esoteric magic, herbal remedies, and practical psychotherapy, often handed down within a family.

People frequently distinguish between diagnostician, herbalist, child specialist, surgeon, obstetrician, and others. In Africa many of the diagnosticians attribute their skill to possession by an acquired spirit, whereas the herbalist's profession and secrets are usually passed on from father to son. Sometimes only certain groups can become healers, as, for example, among the Somalis where only members of the outcast Midgan tribe are eligible.[15]

The status of the medical practitioner is usually high; this may be enhanced by some of the important associated tasks which they sometimes perform, which can include rainmaking, purification ceremonies after "contamination" by such abnormal happenings as lightning or twin births, prophesying the future, and discovering those guilty of crime.[16]

Fees are often, but not always, large. A small engagement fee, in cash or produce, may be given initially and the residue made up on completion of cure. There may sometimes be suspicion of inexpensive or free treatment as being obviously of little value. However, this is not always so, as, in India, homeopathy—an imported nonscientific system of medicine—has taken root and flourished, especially for children, partly because of its cheapness and because the dilute ingredients are thought by parents to be unlikely to harm young patients.

Indigenous practitioners in some parts of

the world have evolved special procedures with regard to fees; thus the *wadad* of Somaliland is assured that his fees will be paid, as otherwise it is known that he may curse his former patient who would then relapse.[15]

In Africa it is also the witch doctor who understands the preparation of medicines used in black magic and poisonings. It is he who can compound a love philter or a death potion. It is, therefore, not surprising to find that many people will calmly say that the ill-wisher gets his medicine for bewitching someone from a medical practitioner. In many groups this in no way detracts from his reputation as a saver of lives unless his behavior transgresses some social custom when he might be accused himself of using his medicines for some evil purposes.

As Read[17] has remarked, however, it is often difficult to classify the precise functions of an indigenous practitioner: "We are caught here, as outsiders, in a fog of confusion about terms and their meaning which only a careful study of linguistics can elucidate. It seems to me that we need to go further in examining their methods and attitudes, since they undoubtedly represent, to the people they serve, a measure of security in the face of disease and danger."

In general terms, nonscientific healers may be classified into two overlapping and indistinctly separated groups: The secular and the magicoreligious. Of the mainly secular type, the Ayurvedic *kaviraj* and the Unani *hakim* represent in India well-organized empirical systems. The former, in particular, has the great emotional appeal of being rooted in the Sanskrit religious writings (*Vedas*) of the ancient sages (*rishis*), as, for example, the Caraka Samhitā.[18]

The second group of indigenous practitioners are those who cure mainly by magicoreligious means. In this category in different parts of the world can be found exorcists, magicians, curers of snakebite, witch doctors, such as the *nganga* of Mashonaland,[16] the *obeah* man of Jamaica, the *wadad* of Somaliland,[15] and the *pawang* of the Malay aborigine.[19]

DIAGNOSIS

Diagnosis is aimed basically at discovering the occult agency responsible and seldom involves careful physical examination or history-taking as in scientific practice, but, particularly in Africa, is often based on divination by throwing cowrie shells, seeds or bones (Fig. 4), which may be carved out of wood or be genuine, as, for example, the talus bones of the lion and koodoo which are highly prized in parts of Rhodesia[20] or by using different forms of trance, crystal gazing, dream interpretation, or possession. Thus among the Fore people in the hinterland of New Guinea Gajdusek and Zigas[3] record that divination to diagnose the sorcerer thought to be responsible for a case of *kuru* is based on the examination of end results of rats that have been roasted in bamboo cylinders.

In some cases a diagnosis by an indigenous practitioner almost precludes scientific treatment; thus in South Africa there are some diseases which are regarded as exclusively Bantu and therefore only treatable by suitably trained witchdoctors. For example, a pediatrician will be making fair progress with the treatment of a case of tuberculous meningitis when suddenly the parents, without an explanation, will remove the child from the hospital. On further enquiry he will learn that a diagnosis of some bewitchment syndrome was made by a consultant called in by a grandparent, or even perhaps by an untrained ward sweeper. Another ethical problem here arises in that some experienced scientific practitioners find that they can attract and hold patients better if they diagnose diseases by indigenous names. This can be perfectly justifiable if it does not at the same time also imply a belief in the recognized etiology, particularly witchcraft, which is inherent in the use of local terms.

Occasionally some form of physical examination may be employed, which is most usually inspectional, but can be bizarre as with the diagnostic "finger-cracking" of the Bakongo.[21] By contrast, diagnosis by the traditional Ayurvedic practitioner of India is made principally by means of the history

and a prolonged palpation of the radial pulse, the right wrist being used for the male child and the left for the female. Three fingers are employed in palpation, one to detect variation in each of the three *doshas*. According to the Ayurvedic view, an observer trained in this specialized palpation of the pulse can judge what food the subject has eaten and the precise number of days a sick person will live.[22]

According to Chatterjee,[22] the acquisition of higher levels of skill in interpreting the pulse requires long diligent practice as well as a "poetic mind," so that the physician who wishes to diagnose a condition simply by feeling the pulse must, like the poet, "produce things very real out of unrealities judged from the material point of view." To the scientific observer some of the criteria for diagnosis seem somewhat vague and difficult to interpret, even when one allows for difficulties in translation. For example, "In cases of vomiting, in wounds caused by the falling of darts, and in the case of suppression of the calls of nature, the pulse moves like an elephant or a goose, as it does in an excess of *kapha* (water)."[22] Nevertheless, many diagnoses are undoubtedly based as much on a shrewd and penetrating observation of the child's general condition, guided by age-old aphorisms and generalizations, some of which are remarkably similar to certain of those attributed to Hippocrates: "He who has long breath and a rattling sound in the breast never survives. He whose nose has dropped down or has dropsy in the abdomen, has no hope of his life. If the eyes become turbid like whey and sunk into their sockets, or if all the senses lose their power, the patient never lives."[22]

TREATMENT

Indigenous practitioners achieve cures as a result of effective practical psychotherapy, herbal remedies, certain physical maneuvers and, as anywhere, by coincidental subsidence of self-limiting disease processes.

The actual forms of treatment practiced by indigenous healers in different parts of the world include the following: dietetic, especially with relation to food taboos, "hot-cold," and similar complex classifications; physiotherapy, including massage, manipulations, different types of bath and poultice;

Fig. 4. Diagnosis by divination by Kikuyu medicine man using thrown seeds. Note fixed attention of little girl seated (Kiambu, Kenya).

physical, possibly sometimes to be considered as a form of "counter-irritation," but usually having a magical aspect as well, including scarification, branding (Fig. 2), cupping, and acupuncture, as well as crude methods of splinting and suture (as with thorns or ant mandibles); medicinal, usually mainly employing empirical herbal remedies; operative, such as the removal of cataracts, piercing of hydroceles with hot iron, circumcision, trephining (as for posttraumatic headache),[23] extraction of Guinea worms, uvulotomy, linear incisions on the tongue, removal of the top of the epiglottis,[15] and tonsillectomy (the excision of a wedge-shaped segment from the center of the tonsils as described in ancient Hindu literature); magicoreligious, including spells, charms, imposition of taboos, incantations and dances, sacrifices and such measures as pilgrimages, and the giving of alms, aimed at expiation, propitiation or ritual atonement, or at "counter-magic."

Excision of the uvula (uvulotomy) is commonly practiced, particularly in childhood, among some groups in East Africa, especially the Kikuyu of Kenya. Jarvis and Mwathi[24] have reported that it is done for a variety of reasons, including persistent irritable cough, pain in the throat, elongated uvula, and anorexia and vomiting. Ill effects appear to be nil, unless the soft palate is damaged inadvertently.

In some regions drastic methods are particularly employed in mental ill health, even in children, as they were in Europe until quite recently. All appear to have the common idea of driving out the demons that are in possession; the particular forms of violence may include beating, icy baths, compulsory fasting, and the use of the smoke-hut.

Frequently therapy can be considered to be twofold, aimed at both the symptoms of the disease and also the alleged supernatural cause. Thus treatment may be multiple, as, for example, with the Yoruba *baba alawo* in Western Nigeria whose treatment may comprise both herbal remedies as well as charms and magicoreligious ritual.

Treatment in some countries may be complicated by a belief in such concepts as auspicious days for commencing therapy, lucky numbers, and traditionally optimal times of day to take medicines. These attitudes may have to be taken into account, for example, when considering how many times a day a medicine should be given and for how long, and may also delay permission to operate on a child with an abdominal emergency.

Medicinal treatment may be administered orally, as infusions, by inhalation or sniffing, by external application (especially into fresh scarifications), by enemas, or intravaginally. In some parts of Africa, "smoking" the newborn baby is practiced in an attempt to make him cough up mucus. As Tanner[14] has commented, medicines so employed may come from vegetable, animal, mineral, or "alien" sources. The last is becoming increasingly common in many places. The indigenous healer is tending to adopt the more spectacularly successful and dramatic scientific remedies, such as penicillin injections, the efficacy of which will be attributed to the associated magical part of the regimen employed.

Therapy may often be based on "sympathetic magic." Thus, among the Somalis, lightly cooked liver is used in the treatment of anemia because of its resemblance to clotted blood.[15] Herbal remedies may be employed because of resemblance of the plant employed to the part of the body involved or to the disease itself, in the same way as medieval pharmacists used the "principle of signatures."[25]

In most forms of indigenous medicine herbal remedies are used extensively. In West Africa, for example, the Fon name for the indigenous doctor is *amawato,* meaning "observer of plants."[26] However, while valuable and potent drugs will be known and usefully employed, probably the majority of the herbals used are inert. This is suggested by analogy by an early seventeenth century *Pharmacopoiea Londiniensis,* which contained 1,028 articles, with a materia medica comprised of 138 roots, 271 herbs, 138 seeds and organs of 116 animals "both terrestrial and marine, and their products,"[27] almost

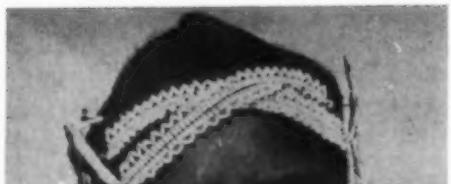

Fig. 5. Zulu girl in ceremonial bead-work finery with empty medicine vial round neck (South Africa).

all of which would be considered therapeutically valueless today.

Some herbal medicines are undoubtedly harmful, especially as they may be prepared in a very haphazard fashion. Thus, occasionally the herbal infusion known as *agbo omo* given to newborn babies in western Nigeria to expel meconium results in severe diarrhea; in Jamaica, Asprey and Thornton[28] have collected and identified over 200 different plants from which "bush teas" are made, some of which have been shown to be responsible for the childhood cirrhosis (veno-occlusive disease of the liver) seen in this island.[29] Other forms of therapy may also sometimes have ill effects, particularly when unclean pastes and powders are applied to wounds, especially the umbilical stump or to fresh scarifications, when tetanus can be a real hazard.[30, 31] Enemas are used in children in parts of Africa and, as irritant fluids including pepper water, may be employed, proctitis, anal fissures, and diarrhea can result.

Herbs and medicines sometimes are given for some direct physiologic effect, but often they are expected to work as a charm, and it is obvious that the medicinal properties of such hardly need further investigation. Thus many Zulu children carry a small bottle of medicine round their necks, but this never is actually taken by mouth (Fig. 5).

Medicinal incisions often indicate past or present symptoms, e.g., children with numerous scars over the region of the spleen in malarial areas. In fact, scarification patterns noted in health surveys of rural children in Africa can be correlated with local disease syndromes and thus give additional approximate insight into childhood disease in the particular area.

The psychological element in treatment is always considerable and diagnoses of witchcraft usually elucidate and treat existing social factors responsible for psychological tensions. A good diviner will always correctly recognize the ultimate cause of psychosomatic symptoms by accusing the person at the root of the tension of the bewitchment. The Zulu have a saying that "the wizard is in the family"; the frequency with which co-wives are accused of a child's illness merely emphasizes that these are relationships likely to be unsatisfactory. Therapy consists of the breaking up this tense relationship by an accusation with consequent banishment, ostracism, or flight of one party and results in cure.

PREVENTIVE MEDICINE

Attempts to prevent illness will, of course, always be based on the local concept of the cause of disease. Logically, these will then mostly be directed against supposedly responsible supernatural agencies, and basically fall into two forms: (a) taboos and the like where something must not be done to avoid evil consequences and (b) active measures where something must actually be done to ensure prevention. Actual measures include charms or amulets (phylacteries) against witchcraft, spirits or the evil eye (Fig. 6), herbal infusions and preparations, propitiation of the gods, conforming to rec-

ognized taboos (such as avoiding eating such spotted creatures as the giraffe and guinea fowl in the prevention of smallpox),[32] adhering to food beliefs, preventing the child from getting too hot or too cold, and so on. In some countries, inoculation from a mild case of smallpox (variolation) is employed, as among the Somalis who use the wrist[15] and the Nyamwezi of Tanganyika who use the bridge of the nose.[32]

In addition, as Davies[33] has pointed out recently, protective inoculation of infants against syphilis (probably of the endemic type) was widely practiced in the Central African Kingdom of Bunyoro-Kitara, up to the 1930's.

Among the organized medical systems, it is of interest to note that Ayurveda stresses the preventive side of health, achieved by attention to diet, exercise, regulated behavior, mental control, and religious observance. In most groups, certain practices will be found which appear to be based on an empirical understanding of hygienic principles. While this may sometimes be so, many apparent "rules of personal cleanliness" are solely religious rites of purification, which happen to coincide with present-day scientific views.

CHILDHOOD CONDITIONING AND HEALTH EDUCATION

It is an undoubted fact that in some countries, especially in rural districts, the less educated portion of the population both prefer and have more faith in indigenous medical methods. To them, scientific medicine is still strange and incomprehensible, and, at the same time, it takes little or no cognizance of local ideas concerning disease and is often practiced by someone whose socioeconomic condition, education, and even language is far removed from the average peasant. Again, the indigenous healer is often meant to be able to diagnose illness by his mysterious omniscience, so that, by comparison, the scientific doctor's detailed enquiry into the history may sometimes cause doubt to be cast on his skill.

All over the world attitudes toward medical beliefs are in transition, or, at least, in the process of modification.* As facilities for modern pediatrics improve and become more available as, for example, by the development of rural health centers, so it is likely that

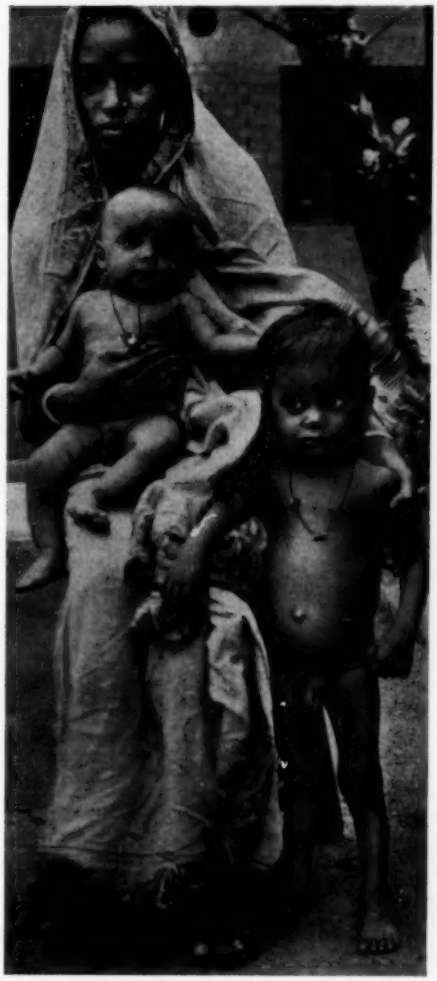

Fig. 6. Bengali children showing charms round neck (*maduli*), black spots on forehead, and black outlined eyes intended as protection against the evil eye. (Vermilion spot on mother's forehead unconnected) (West Bengal, India).

*Modification may also occur in the form of occult practice employed. Thus, among the Fanti of Ghana, new cults, including the widespread one known as Tigari, have developed recently in which the witch-finding ritual reflects influence from both Christian and Muslim sources.[34]

Fig. 7. Hausa witch doctor. Note attention of boys in audience (Ibadan, Nigeria).

Fig. 8. Magical curing ceremony among the Wakamba. Bewitched patient is under blanket inside magical area, which contains various ritual items, including a snake in a large gourd. Note attention of children in shade by hut (Mackindu, Kenya).

more people will have the opportunity and will become willing to bring their children for scientifically rational medical treatment. It seems certain that, as past experience has already shown, this will occur at first with the diseases for which there are dramatic, cheap, easily effected, and certain cures, such as yaws, malaria, scabies, and ascariasis.

As noted earlier, quite frequently a dichotomy may develop whereby some types of illness are thought to be curable by scientific methods, often including certain infectious diseases, while others continue to be regarded as being due to supernatural causes and in need of indigenous treatment. Quite often a patient may attempt to use treatment from several different systems at the same time, as, for example, a village child in West Bengal, whose cholera was treated by intravenous fluids and oral homeopathic medicines, together with the use of *maduli* (charms) and the propitiation of the appropriate goddess.

The deep-seated ideas concerning disease and conversely the difficulty of affecting views by health education is best understood when it is realized that from early childhood belief in witchcraft and magic is being continuously inculcated, so that every illness becomes a learning situation (Figs. 4, 7, and 8). Few children have not heard the family discussing death and illness, and ritual and taboo are made part of the daily life. Small wonder that hygiene lessons in school appear to make no impression on children when they are being taught ideas that are sometimes completely incompatible with what they learn at home. Until the life at home is changed substantially, teaching of scientific hygiene often will continue to be essentially confusing and contradictory for children. This is one reason why health education of the *community*, and not only for one section of the population, is so important; group discussions are more effective than lectures, as they give an opportunity for parents to air their views and for inconsistent and incompatible ideas to be cleared up.

CASE HISTORY

Thokozile, a 12-year-old pubescent Zulu girl, complained of a toothache 1 day on return from school and later developed hiccoughs. Her parents, realizing the gravity of these symptoms sent for the family practitioner, a herbalist. It was he who had provided the medicines for smoking the child at birth, had shrewdly advised weaning from the left breast when it had been turned poisonous by bewitchment, and had treated her successfully for numerous childhood ailments. He demanded an engagement fee and he then took a brief history. Having no large audience to impress, he proceeded with

symptomatic treatment without making a definite diagnosis. Inhalation of the smoke of medicines sprinkled over coals proved successful.

Next day, however, the patient lay mute and did not recognize her parents. Again Nsimbi the *inyanga* (herbalist) was called in and several neighbors also came to enjoy the drama. Bones were thrown and with much interpretation (assisted by the reaction of the parents) a diagnosis of "dumb" *fufunyana* was reached. This is a possession by an evil spirit sent by an ill-wisher and is a serious condition requiring specialist attention. The family practitioner recommended that Thokozile should be taken to a distant female diviner-herbalist, who was establishing a reputation for curing this illness.

She was taken to her in an ox-drawn sleigh and, after an engagement fee *(ugxa)* of £5 ($14), this witch doctor confirmed the diagnosis and proceeded with the next step of making the spirit in possession declare its nature. Smoking, scarification of Thokozile's shadow and of the girl herself, and force-feeding of laboriously compounded medicines continued until the *fufunyana* "opened" and confused sounds came from the girl. This was interpreted as Shangaan, the language of a distant tribe and the diagnostician could now describe the cause. Someone had bewitched the girl with a mixture of human fat, ants which had congregated on a pigeon's heart placed on a Shangaan's grave, and the urine of a deaf mute. This concoction might have been deliverd to Thokozile at night by the bewitcher's animal familiar or *tikoloshe* (an ape-like, hairy being with an enormous penis) or, worse, it might have been placed on a path to their home, in which case the parents might also be incubating the illness. Charms for their protection were therefore necessary and were thoughtfully provided for £2 ($5.60) each by the practitioner.

All the skilled treatment of the *isangoma* (diviner-herbalist) only made the *fufunyana* spirit more active in the girl. It sang in foreign tongues, it made her run about, it made her spend hours scrutinizing feathers plucked from passing fowl; hyperventilation and tetany developed, but it refused to leave her.

Next the mother's minister of religion (the father was a pagan polygamist) persuaded them to take the girl to his home to be prayed for. But his prayers and those of the women's club of the church, holy water, and the Bible also failed. After 2 weeks, the priest suggested that the local clinic be tried, as it was just possible that after years the doctor there had learned something about this Bantu disease.

Physical examination at the clinic revealed nothing except a carious tooth and many recent medicinal incisions. Thokozile also became quiet when placed in the sober, clean, and foreign atmosphere of the consulting room. A diagnosis of *fufunyana* was made, this being the only appropriate name for this local culturally determined variation of hysteria. Investigation of the patient's home by a social worker revealed the foregoing history and the fact that the father had 3 wives. Treatment by discussion, suggestion, and placebo failed. The family soon perceived that this was a disease for which Europeans could do nothing and they left the locality.

It later transpired that Thokozile had recovered completely after her parents had visited the great specialist *fufunyana,* Nxole, who lived 30 miles away but who had no doubt been studying their case and its environment in anticipation of its inevitable gravitation to him. At a well-attended smelling out ceremony (punishable by law in South Africa but still performed for big fees), he diagnosed, by invoking his special personally possessed spirit, that the girl had been bewitched by the youngest co-wife of the mother. Thokozile's mother agreed, saying that this new wife wanted her own children to get more financial support from the father for schooling and that, therefore, she would be likely to try to kill Thokozile from jealousy and to eliminate competition. As this new wife was a Mosuto, married to the father when he was working as a migrant laborer, the neighbors also feared her, so it

was a relief to all when she was accused of witchcraft and ejected from the locality. Everyone was satisfied with the correctness of the diagnosis. The specialist prescribed herbs and also recommended that the family move to another house for 6 months and observe certain taboos. He was paid an ox worth £15 ($42) and 2 goats (£6 or $16.80) for his services.

The wisdom of this socially oriented treatment and diagnosis was further appreciated later when a young teacher mentioned to one of the clinic's social workers that he had been a secret lover of the banished wife, not knowing that she was a witch. It also became known later that this teacher had been seducing girls in his class, including Thokozile, for the Zulu premarital external type of intercourse, and it is likely that the young wife knew this and resented it.

In retrospect it is probable that tension between this woman and Thokozile and also the girl's affair with her teacher (for which she was too young even by Zulu standards) had precipitated the hysteria. It is interesting to speculate how much of this syndrome was learned in early childhood by observing other cases and how much of it was suggested by the indigenous medical practitioners themselves during the course of the illness.

CONCLUSION

The correct long-term attitude toward coordination between a scientific and a traditional medical system undoubtedly has been expressed by Jawaralal Nehru, the Indian Prime Minister, when he gave his opinion that "it would be foolish to look down on the Ayurvedic and Unani systems [and he asked delegates] to take the good in these systems and incorporate them in a scientific way into the general practice of medicine in the country." In other words, present-day scientific medicine, with its ultimate roots in knowledge from all over the world and its recent rapid impetus from the Western world, should investigate dispassionately the various systems so that the useful in each may be incorporated into an enriched, expanded, and truly global system. Examples of past adoptions from herbal practitioners all over the world are well known and include quinine, digitalis, ephedrine, cocaine, morphia, curare, and strophanthus, which was reported by David Livingstone 100 years ago as being employed in the Zambesi area as an arrow poison.[35] More recently the active principles of *Rauwolfia serpentina,* which had been employed for thousands of years as a sedative by Ayurvedic practitioners have been shown to be extremely useful in the treatment of hypertension. Similarly, in Britain raspberry leaf tea, a traditional "old-wives" potion after delivery, has been shown to contain a pharmacologically potent inhibitor of uterine activity.[36]

As stressed by Wild and Gelfand,[25] there is, at least in some places, urgency in the need for this type of investigation as herbal lore is beginning to be lost. They describe an interesting field approach carried out in Mashonaland in Rhodesia in which a team composed of physician, botanist, and *nganga* (herbalist-witch doctor) attempted to discover and identify allegedly therapeutic plants, for later pharmacologic testing.

Similarly, there is a real need for the scientific investigation of traditional forms of physical therapy, such as the various forms of baths, massage, spa treatment, and the Chinese techniques of acupuncture and moxibustion,[37, 38] as well as the bases for the numerous psychotherapeutic procedures employed and their actual techniques. Examples would include the scientific study of the psychodynamics and physiologic effects of *Yoga* (which is usually commenced in childhood) and of various forms of "possession."

In conclusion, it is hoped that these brief notes on some aspects of indigenous medical systems may serve to emphasize their vital importance to the practical child health worker. This type of knowledge is necessary because (a) it leads to understanding of behavioral and environmental factors underlying disease patterns existing in communities, (b) it gives insight into people's values, knowledge, and attitudes to health and dis-

ease, (c) it determines how to ensure maximum cooperation, participation, and appreciation from a population for health work carried out by personnel trained in a foreign, that is, scientific, medicine, and (d) it may enable scientific pediatrics to become enriched by new ideas, methods, drugs, and techniques.

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MEDICAL PROGRESS

The present state of knowledge on the celiac syndrome

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THE EARLY historical background of the celiac syndrome has been described fully by Sheldon[1, 2] and there is no necessity to repeat it here. The object of this paper is to give critical consideration to recent developments in this field, to review the boundaries of present knowledge, and to put forward some ideas for discussion and possible development.

CLINICAL CLASSIFICATION AND DIAGNOSIS

Diagnosis should begin in the clinic. One may, therefore, start with a rather broad clinical classification—the celiac syndrome. This may be based usefully on the criteria originally expounded by Gee[3] in 1888. He introduced the term celiac disease, now modified to celiac syndrome, to denote a clinical state in children associated with wasting, muscular atony, abdominal distention, anemia, retarded growth, and the passage of pale, bulky, offensive, fatty stools.

It is of the essence of a clinical classification that it varies in scope with each observer. Thus, some may insist on the presence of all or most of these cardinal features, while others may be prepared to make the diagnosis on the basis of one of them. Unfortunately, the classification of patients with the celiac syndrome is sometimes made in the absence of any of Gee's diagnostic criteria; this is liable to cause some confusion.

Fibrocystic disease of the pancreas was differentiated from the rest of the celiac syndrome more than 20 years ago.[4] Nevertheless, it is still useful to include in this discussion a consideration of pancreatic enzyme deficiency, since it occurs independently of fibrocystic disease of the pancreas. It is helpful to compare the features of this group with others.

LABORATORY AIDS TO DIAGNOSIS

An experienced observer may well carry the diagnosis further on purely clinical grounds, but, for the majority, laboratory

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aids enable a more refined diagnosis, based on etiology, to be reached with greater certainty. A number of studies have been shown to be of value in arriving at the correct final diagnosis and these will be briefly discussed, since they have some relevance to later considerations.

Fecal fat. The daily fecal fat output should be measured. The method generally used currently is based on the daily fatty acid method of van de Kamer and associates.[5] Provided that the intake of fat is between 50 and 120 Gm. a day and consists of ordinary dietary fats, there is little need for more accurate assessment. In very young children, measurement of intake is relatively simple and should be done. The daily, long-chain fatty acid output should be averaged over at least 4 consecutive days, preferably more. If measurement of intake is only approximate and the proportion of fecal fat derived from other sources than dietary fat is unknown, it is best to express the result of grams as fecal fat per day. Under such circumstances, conversion to a percentage absorption figure introduces unnecessary errors and adds nothing. If labeled fat is used, percentage absorption may be assessed more satisfactorily.

Other features of the stools. The stools should always be seen. They may be fluid or semifluid and the volume may be increased. They are usually pale in color and the nitrogen and volatile fatty acid content may be higher than normal. However, these changes are not always present; long-chain fats may be significantly increased in stools that look normal.

Examination of small intestinal contents. Samples of the contents of the upper small intestine are withdrawn by intubation, the position of the tube being checked radiographically. The contents are examined for pancreatic enzymes, bile salts, and organisms. A stimulus to pancreatic secretion, such as secretin, should be given. Pancreatic enzymes should be studied individually, since single enzyme defects may occur.[2, 6] Standard methods may be used.

Demonstration of enteropathy. The presence of an enteropathy affecting the small intestine can be demonstrated in many patients with the celiac syndrome. The investigations required to establish this are absorption rate tests, radiography, and biopsy.

Absorption rate tests. The rate of absorption of glucose, xylose, or other water-soluble index substances can be assessed by measuring the rate of accumulation in the blood or excretion in the urine. It is obvious, of course, that the blood levels achieved are dependent upon the relative rates of income and removal. The rate of absorption is not solely dependent upon the absorptive capacity of the small intestine, since it may be affected by delayed gastric emptying. The rate of removal differs from patient to patient and may not remain constant in the same patient during the experimental period. Urinary excretion may be affected by renal function. These factors may make interpretation difficult and have prompted many investigators to use more than one type of test in assessing the rate of absorption. Many suitable methods are available. It must be emphasized that these tests only measure rate of absorption. There is nothing inherently incompatible about the simultaneous occurrence in a patient of a depressed rate of absorption of glucose and almost complete overall absorption of glucose with consequent nutritional benefit.

The absorption rate of fat or a fat-soluble index substance must also be studied. A number of satisfactory methods are available which indicate the rate of absorption of visible particulate fat.

Radiography. Many patients with the celiac syndrome show gross clumping of barium sulfate when a simple suspension of this opaque medium in water is used. This appearance is, however, not uncommon in normal children, although usually to a lesser degree. This effect is due to the flocculation of barium sulfate by excessive amounts of mucus.[7] This is borne out by the fact that clumping is not seen if a nonflocculable barium sulfate preparation is used. The administration of a nonflocculable opaque medium reveals the true appearance of the

small intestine. Attention should be paid to the mucosal pattern and to the size of the intestinal lumen.[8]

Biopsy. Biopsy specimens of the small intestinal mucous membrane may now be obtained by intubation.[9, 10] The length and shape of the villi, the characteristics of the intestinal columnar cells covering the villi and lining the crypts, the amount of cellular infiltration, and the condition of the blood vessels and lymphatics are all points of interest. Care must be taken in the accurate orientation of the specimen.

INTERPRETATION OF LABORATORY FINDINGS

Confirmation of the general diagnosis of the celiac syndrome. In the study of any syndrome, it is advisable to have some sheet-anchor in the form of a measurable feature that can be regarded as a sine qua non for diagnostic purposes. In the case of the celiac syndrome, the level of fecal fat is probably the safest guide, since it appears to be a good index of depressed intestinal absorption and it is relatively easy to measure. On this basis, an average output of fecal fat of less than 5 Gm. a day on a daily fat intake of more than 50 Gm. may be taken to exclude the diagnosis of the celiac syndrome. In this condition, the fecal fat output exceeds 5 Gm. a day and commonly averages more than 10 Gm.

Pancreatic enzyme deficiency. The fecal fat in patients with deficiency of pancreatic lipase is commonly greater than that observed in other forms of the celiac syndrome.[11] The percentage hydrolysis of the fecal fat may not differ from that observed in patients with normal pancreatic enzymes. The volume of the stools is often large. The definitive test for this group is the direct examination of samples of intestinal contents for the presence or absence of lipolytic activity, which is best studied with long-chain fat as the substrate.[12]

Many patients with pancreatic enzyme deficiency show no evidence of enteropathy as judged by absorption rate tests for water-soluble index substances, radiography, and biopsy. The absorption of visible particulate fat, however, is completely suppressed if unemulsified fat is administered.[13] It is obvious that patients who pass a large volume of stools each day may develop water and electrolyte imbalance. This may cause a secondary enteropathy. Such effects should not be allowed to obscure the essential principles involved in the differential diagnosis of the basic lesion.

Bile salt deficiency. Both pancreatic lipase and bile salts are necessary for normal fat absorption. It is, therefore, advisable to examine the small intestinal contents for bile salts; bile pigments may also be measured as an indication of the presence of bile. Bile salts are occasionally deficient and may account for the faulty absorption of fat.[14]

Small intestinal infestation. The upper small intestinal contents are normally sterile, or nearly so. In the celiac syndrome, organisms may be present, but this is not a common or a constant finding.[15] Their significance remains obscure. Occasionally large numbers of Giardia are observed and these may give rise to a great increase of secretion of mucus and interference with absorption. Infestation of the upper small intestine by Giardia must be considered as a possible cause of celiac disease.[16, 17]

Gluten-induced enteropathy. Generalized depression of the rate of absorption of both water-soluble index substances and fats, abnormal radiographic appearances in the form of dilatation of the intestinal lumen, a "stacked coin" appearance when a non-flocculable opaque medium is used, changes in the histologic appearance of the upper intestinal mucosa indicated by shortening or clubbing of the villi, abnormal appearances of the columnar cells, and marked cellular infiltration indicate the presence of an enteropathy. Such an enteropathy affecting the upper small intestine is commonly due to intolerance to wheat gluten. If such a situation is demonstrated by the studies suggested and the examination of the intestinal contents has revealed that pancreatic lipase and bile salts are within normal limits and that there is no gross infestation with

Giardia, a period of trial on a gluten-free regimen is indicated. This should be enforced strictly and involves major changes in the patient's diet.[18]

The fact that a patient improves, or even recovers completely on a gluten-free regimen, does not in itself justify the diagnosis of gluten-induced enteropathy. It is essential, when remission has been established and when the fecal fat output has come down to normal or near normal levels, to reintroduce gluten into the patient's diet. The demonstration of an unequivocal increase of fecal fat to abnormal levels may be regarded as a definitive test for gluten-induced enteropathy.[19]

Other conditions included under the clinical diagnosis of celiac disease. By the use of the investigations described, it is possible to differentiate patients with pancreatic enzyme deficiencies, bile salt deficiency, upper intestinal infestations such as moniliasis or giardiasis and gluten-induced enteropathy. Who is left from the original group of patients with the clinical diagnosis of celiac disease in whom an increased fecal fat output has been confirmed in the laboratory?

As already stated, there is no reason to suppose that all patients who benefit from a wheat gluten–free regimen are suffering from gluten-induced enteropathy. It is obvious that those suffering from any form of allergy to wheat protein might be expected to benefit from a wheat protein–free diet. The full therapeutic implications of the dietary changes involved in the institution of a gluten-free regimen are difficult to assess. A recent report from Sheldon,[20] in which only 23 of 95 celiac patients successfully given a gluten-free diet showed evidence of deterioration when gluten was reintroduced, strongly suggests that some effect other than relief of gluten-induced enteropathy may be concerned. As Sheldon[20] states, "it seems unlikely that intolerance toward gluten offers a complete explanation of celiac disease." Included by some in the diagnosis of the celiac syndrome may be groups of patients who benefit from the introduction of a wheat gluten–free regimen but are not suffering from gluten-induced enteropathy as here defined. The validity of this hypothesis could be examined by the regular application of the definitive test for gluten intolerance[19] when the first remission is established on a gluten-free regimen.

A further possibility is suggested by the differences of opinion expressed in the literature about the permanence of gluten intolerance. There is little doubt from studies in adults that wheat gluten intolerance may persist for long periods of time without obvious decrease in intensity.[19, 21, 22] It has been shown that many former celiac patients remain sensitive to gluten although they had been regarded as clinically recovered from celiac disease.[23] On the other hand, Sheldon's observations suggest that a considerable proportion of patients with celiac disease lose their gluten intolerance. We have had a similar experience. One of the 28 celiac patients of an earlier study[14] was subsequently found to tolerate gluten normally; this patient had not, however, been specifically tested for gluten intolerance after his first remission. As already pointed out, some of these patients may never have had gluten intolerance but may have benefited from the gluten-free regimen for other reasons. Some, however, may have had gluten intolerance from which they have recovered. If gluten intolerance is due to an intestinal enzyme deficiency, a matter that will be discussed further later, the existence of both a permanent and a more transient defect might be expected. An underlying genetic fault might well produce a permanent enzyme deficiency, but damage to the intestine, for example, by enteritis might only produce a transient inadequacy. The re-establishment of the integrity of the intestinal mucosa in the former case should not affect the gluten intolerance, but in the second it is likely to be accompanied by re-formation of normal enzymes, with consequent disappearance of the gluten intolerance. Finally, consideration must be given to the possibility of gradations in gluten tolerance. Difficulties might arise during a period of temporary disequilibrium and the ensuing damage to the intestine might

give rise to a vicious cycle, the breaking of which by a gluten-free diet might allow equilibrium to be re-established on a moderate gluten intake. If such differences exist, it is important that the facts be established, since they are relevant to other research investigations and to treatment.

If all patients who respond favorably to a gluten-free regimen, irrespective of the cause of the benefit, are excluded, there still remains a small number of patients who do not appear to fit into any of the categories so far described. Some of these may present with severe hypoproteinemia and edema. This may result from leakage of protein into the intestinal lumen. If this occurs high up in the intestine, the protein may be digested and absorbed and there may be no apparent loss of nitrogen. The leakage may be revealed by the parenteral administration of labeled polyvinylpyrrolidone (PVP), which cannot be digested and reabsorbed and therefore appears in the stools.[24] These patients may show dilated lacteals on biopsy and lymphatic stasis may be the cause of interference with fat absorption. Other types of lymphatic blockage may be seen; rarely celiac disease may result from tuberculous enteritis[25] or other diseases affecting the small intestine. Such patients are relatively rare and each case must be investigated and treated on its merits.

PATHOGENESIS

The characteristics of the celiac syndrome may be broadly grouped as alimentary effects, associated with faulty absorption, psychological effects, and growth effects.[20]

Alimentary effects. *General characteristics of the stools.* The characteristic features of the stools of celiac patients are due mainly to the action of the intestinal flora in the lower parts of the intestine. It has been shown that the output of fecal bile pigment in these patients is within normal limits, or may even be increased,[26] and that the pallor of the stools may be due to the reducing action of the flora.[27] The formation of increased quantities of steam-distillable, short-chain fatty acids may be attributed to the fermentative action of the intestinal flora on unabsorbed carbohydrate. The increased volume may be brought about by the large number of small water-soluble molecules produced by fermentation. In pancreatic enzyme deficiency, in which carbohydrate absorption may be more seriously affected, a striking increase in volume of the stools is often observed. Correction of the basic fault by appropriate therapy usually results in a rapid disappearance of the effects of these secondary floral changes.

Nature of the long-chain fat in the stools. It has been known for some time that the excess fecal fat of celiac patients consists of a relatively high proportion of saturated fatty acids.[28, 29] This has been borne out by recent detailed studies using vapor phase chromatography. Fecal fats contain a remarkably high content of stearic acid[30]; oleic acid isomers and hydroxy fatty acids have also been demonstrated.[31] The general proportions of the various fatty acids in the excessive fat in the stools of celiac patients closely resemble those of normal fecal fat. The reason for the peculiar composition of fecal fat is not yet known; it is probable that the intestinal flora plays some part in determining the nature of the final product.

Origin of the fecal fat. The fat in the stools may be derived from unabsorbed, dietary long-chain fat or from other sources. These two fractions of the fecal fat are often referred to as the dietary and the nondietary components, respectively. These terms can be misleading since the nondietary component may be derived from dietary material other than long-chain fat. If this point is appreciated, however, the terms may be used conveniently.

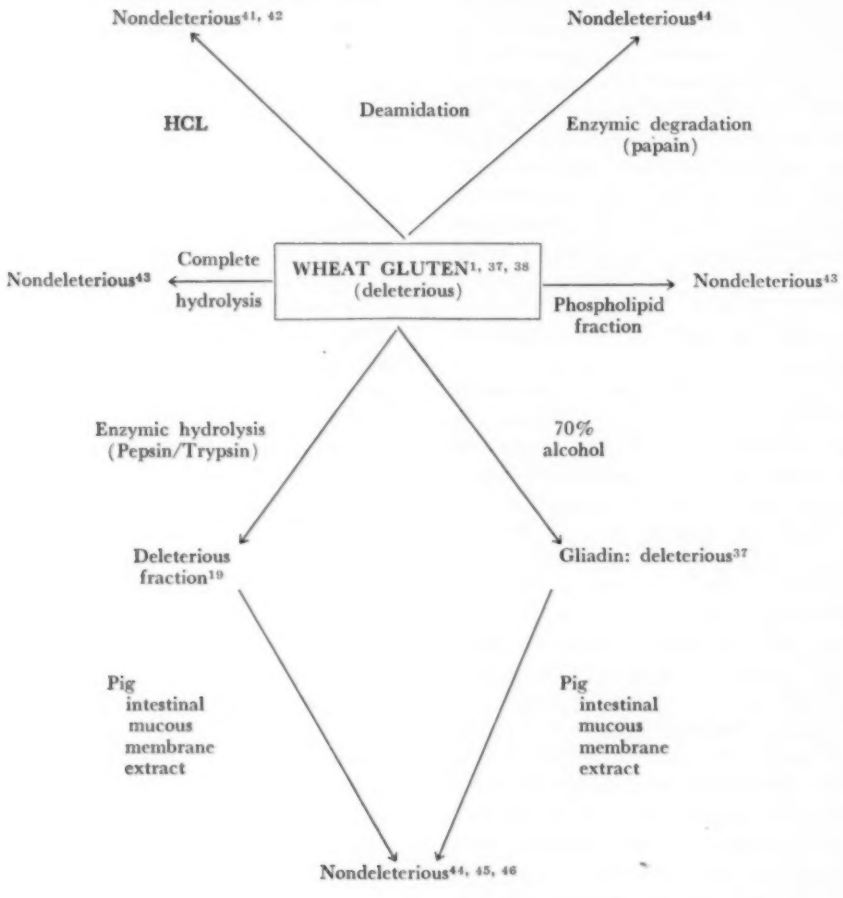
From studies on fat loading and deprivation and use of labeled fats, it seems clear that most of the increased fat in the stools of a celiac patient is derived from unabsorbed dietary fat.[32, 33] The demonstrable enteropathy in these patients presumably accounts for this interference with absorption. There may also be an increase of the nondietary component; this may be accounted

for at least in part by the increased bacterial growth within the intestinal lumen. Occasional cases occur in which the increase of the nondietary component appears to be much more significant.[29] A similar situation has been described in certain patients with tropical sprue.[34] This has been attributed to an abnormality in saturated fatty acid metabolism.[29] It is doubtful whether sufficient information is available at the present time to attempt an explanation of this peculiar situation. Further studies with labeled materials and detailed analysis of the fatty acids present should, in due course, provide the answer.

The fat absorption fault in pancreatic lipase deficiency. The characteristic features of the uncomplicated case of pancreatic lipase deficiency are a marked fat absorption defect and a flat chylomicrograph.[13] If other pancreatic enzymes are also deficient, there may be a great increase of fermentative activity in the stools and an increased loss of nitrogen. Again, provided that there are not complications of electrolyte imbalance or edema, the small intestine remains unaffected and the rate of absorption of water-soluble index substances is within normal range. The faulty absorption of fat may be attributed to faulty emulsification in the intestinal lumen. This is borne out by a simple experiment. If finely emulsified fat is introduced into the duodenum of such a patient, a normal systemic hyperlipemia rapidly develops.[2, 35]

Gluten-induced enteropathy. *Nature of the deleterious agent.* The deleterious action of wheat flour in patients with celiac disease was originally observed by Dicke.[36] The differentiation between wheat starch and wheat gluten in their effects on celiac patients was established by van de Kamer and colleagues,[37] who also claimed that gliadin was entirely responsible for the deleterious action of wheat. However, Sheldon was unable to confirm the difference between gliadin and glutenin. Working independently, Anderson and co-workers[38] confirmed the deleterious effect of wheat gluten in celiac children and were able to demonstrate the effect of removal and reintroduction of wheat gluten on the main features of the enteropathy as observed in many celiac patients. Further confirmation was also provided by Sheldon and Lawson.[1] Since that time extensive further confirmation has been provided by other workers in many different parts of the world. Wheat, rye, and oats were found to be harmful by the Dutch workers,[39] but in England oats did not appear to be injurious.[2, 38, 40] The reason for this discrepancy is unknown. Deamidation of gluten or gliadin by acid treatment reduced the deleterious properties.[41, 42] Complete acid hydrolysis gave a product that was harmless to celiac patients.[43] Enzymatic hydrolysis of gluten with pepsin and trypsin and subsequent ultrafiltration and autoclaving yield a fraction that is as deleterious as the original gluten.[19] However, papain detoxicates the gluten or gliadin, probably by deamidation.[44] Incubation of the autoclaved ultrafiltrate of a peptic/tryptic hydrolysate with pig intestinal mucous membrane extract yields a product that is much less deleterious.[45, 46] This modification does not, however, involve deamidation.[47] The present situation is indicated in Table I. These fractions have been tested in patients. This involves the preparation of quantities of each fraction corresponding to a daily dose of 10 Gm. of gluten; enough must be available to carry on for periods up to 21 days in case of a negative response. The patients must be in remission and, of course, they or their parents must be fully aware that the test may cause a temporary return of celiac signs or symptoms. The immensely cooperative spirit of both patients and parents in connection with these studies, which are made in the interests of more complete knowledge of celiac disease and, it is hoped, more effective treatment, deserves appreciative recognition. With these difficulties to contend with, it is not surprising that many of the conclusions recorded in Table I are based on observations that have not been repeated extensively. Nevertheless, there is close agreement on most points among the different groups of investigators involved.

Table I. Effects of gluten fractions in patients with gluten-induced enteropathy



Present information indicates that the deleterious agent is a relatively low molecular weight, heat-stable, ultrafiltrable substance (or substances), resistant to peptic/tryptic digestion, but destroyed by enzymes present in pig intestinal mucosa, or by a deamidase, such as papain. It occurs in wheat gluten and appears to be transferred readily with the gliadin fraction. There is some evidence that it is not included in the phospholipid fraction.[43] It is closely associated with and may be a peptide (or peptides).

Effect of the deleterious agent. If it is accepted that some substance contained in the gluten fraction of wheat flour is responsible for the changes in these patients, the next question must be: what does it do and how does it do it?

So far as the small intestine is concerned, two changes are evident. First, mucosal damage and, second, a defect in motility. It seems probable that the delayed rate of absorption observed and the over-all defect in absorption of fat may be attributed to one or both of these effects.

The damage to the mucosa varies from shortening and clubbing of the villi to a sticking together of groups of villi so that their individual structure barely is discernible. This disorganized mass of villous tissue may be heavily infiltrated by plasma cells

and other round cells. The absence of separate discrete villi has been interpreted by Doniach and Shiner[48] as villous atrophy and the tissue described above as disorganized villous tissue has been regarded by these observers as overgrown crypts. Adults with a deficiency of folic acid also display these mucosal changes and overgrowth of the crypts would seem unlikely under these circumstances. A lining layer of cells can usually be seen; these may be abnormal in appearance, with displaced and enlarged nuclei. Several investigators have reported on the slow rate of recovery of the mucosal changes and lack of correlation with the extent of malabsorption.[49, 50, 51] These observations would suggest that the mucosal changes are not the main cause of the absorptive difficulties. Although there is not yet sufficient evidence to show whether the changes observed are completely reversible, it is apparent that the recovery of functional activity of the small intestine occurs before there are obvious signs of improvement in the state of the mucosa. Motility of the intestine, on the other hand, might be prevented or restored more quickly than changes in the mucosa and might also play an important part in the absorptive mechanism. It was shown, at an early stage, that the radiographic changes, involving dilatation and hypomotility of the small intestine, improved rapidly on a gluten-free regimen and were among the first signs to return when gluten was reintroduced into the diet.[38] There are, therefore, some grounds for considering that changes in motility may be the key to the effect of wheat gluten in gluten-induced enteropathy.

Mechanism of action of the deleterious agent. The mechanism of action of gluten is likely to be either allergic or more directly toxic. Thus it might exert its action indirectly by some form of antigen/antibody reaction affecting the intestinal epithelial cells or musculature or it may act more directly as a pharmacologically active agent. Each of these possibilities must be considered.

The allergic hypothesis. Several features of the celiac syndrome might be attributable to allergy. It should, perhaps, be pointed out that the term "allergic" is being used here in a relatively strict sense to imply a mechanism involving some type of antigen/antibody reaction. The term "allergic" is sometimes used to indicate no more than that the removal from the diet of the substance to which the patient is "allergic" results in improvement of the patient's health. In this sense, of course, patients with gluten-induced enteropathy are "allergic" to wheat gluten. Whether they have some antigen/antibody reaction is much more difficult to determine.[52] The restriction of the effect to wheat and rye, the excessive mucus secretion, mucosal damage, and response to corticosteroids might fit in with some form of allergic response to a constituent of wheat or rye gluten. Resultant delay in absorption might give rise to secondary floral changes, which could, in turn, result in the formation of the characteristic stools. The close association of wheat and rye in other immunologic reactions is also suggestive. Against this, however, are the following facts: no cutaneous sensitivity to gluten can be demonstrated,[43, 46, 53] the effects on motility of the intestine are different from those observed in allergy, antihistaminic drugs are ineffective in treatment, and other classical allergic phenomena are not commonly observed in celiac patients or their relatives. More recently it has been demonstrated that guinea pig tissues sensitized to gluten (Dale-Schuster preparation) do not respond to the autoclaved fraction obtained after peptic/tryptic digestion, although this material is fully effective in patients with gluten-induced enteropathy.[19]

In spite of these facts, however, a number of observers continue to regard the effect of gluten in gluten-induced enteropathy as essentially allergic in nature.[54, 55, 56] In particular, Berger[57, 58] has demonstrated differences in antigen/antibody reactions between normal and celiac patients. In the celiac patient there was a reduction of circulating cereal antibodies after feeding gliadin; this did not occur in normal individuals. It must be doubted whether this evidence alone can be regarded as a true indication that allergy

plays a significant part in the pathogenesis of gluten-induced enteropathy. Even if the occurrence of this phenomenon was established firmly in a series of patients with proved gluten-induced enteropathy, it might still be only a concomitant change, unrelated to the cause. In the absence of any evidence of a localized antigen/antibody reaction that might account for the mucosal damage, or other potentially significant effect, it is impossible to attribute any etiological significance to these immunologic responses. Apart from this, it already has been indicated that the mucosal changes observed may not be of primary importance.

Nevertheless, the consideration of allergic phenomena in relation to the celiac syndrome may be important. In a condition in which the intestinal mucosa is severely damaged and protein digestion may be incomplete, the risk of development of secondary allergic reactions is apparent. There are reports[59, 60] of celiac patients apparently developing sensitivity to milk proteins or other food materials. We have had similar experiences. It is not clear at present whether these represent a primary allergic sensitivity or whether this may have developed as a secondary phenomenon in an individual whose small intestine is already damaged. Further study of such phenomena is needed. It is also possible that gluten-induced enteropathy is merely an example of a type of metabolic fault that may involve a wider range of food materials, the effect depending upon the nature of the food protein on the one hand and the enzymic or metabolic defect on the other.

The toxic hypothesis. We have been particularly interested in this possibility during the last few years. The most interesting recent development has been the demonstration that the same autoclaved, ultrafiltered fraction, derived from the peptic/tryptic digest of gluten, that is deleterious in celiac patients, causes inhibition of the peristaltic movements of isolated rat or ginea pig intestine.[61] As already described, dilatation and hypomotility of the small intestine are observed when gluten is reintroduced into the diet of a celiac patient in remission on a gluten-free regimen.[88] The pharmacologic analysis of this effect is also of interest. The inhibitory action is observed if the fraction is applied to the outside of the intestine, but it does not occur if the material has to pass through the normal mucous membrane. Incubation with an extract of the mucous membrane also destroys the inhibitory action; the effect appears to be enzymic. The nature of its inhibitory action has also been analyzed and it has been shown to inhibit the production of acetylcholine.[62] Work is in progress to determine whether the characteristics shown in isolated tissue preparations can also be demonstrated in celiac patients. It is interesting that Ingelfinger and Moss[63] reported many years ago that the intestine of a patient with nontropical sprue gave a better motility response to methacholine than to eserine; we endeavored to repeat this a few years ago, but without much success. These studies were, of course, carried out long before the significance of wheat gluten in these conditions was appreciated. A lot of further work is needed on these problems, but there is no doubt that serious consideration must be given to the direct toxic hypothesis.

Nature of the basic metabolic fault. It is apparent that the celiac patient handles wheat gluten differently than does the normal individual. No differences in gastric or pancreatic digestion have so far been demonstrated and peptic/tryptic digestion of gluten in vitro does not result in detoxication.[19] Among the main effects observed in patients with gluten-induced enteropathy are mucosal and motility changes affecting the upper small intestine. It seems likely, therefore, that the detoxicating mechanism lies either in the lumen of the intestine or in the intestinal mucosa itself, although its location in the liver or elsewhere cannot be excluded entirely. However, experimental studies have shown that treatment of the deleterious agent with an extract of intestinal mucosa results in detoxication, an effect that is destroyed by heat.[19] A similar destruction by mucous membrane extract of the agent inhibiting intestinal peristalsis has been shown and the

inhibitory substance is no longer effective if it has to traverse the normal mucous membrane to reach the muscle. The same substance causes depression in the production of acetylcholine in isolated intestine; this effect is prevented also by incubation with mucous membrane extract.[62] All these observations are compatible with the view that an enzyme (or enzymes) is present in the normal small intestinal mucosa that renders the deleterious agent present in the wheat gluten fraction innocuous. The obvious assumption is that such an enzyme is deficient or inadequate in the mucous membrane of a patient with gluten-induced enteropathy. There is, however, no direct evidence to support such a hypothesis at the present time.

One other line of evidence that might have some bearing on the basic metabolic fault is provided by the observation[64, 65] that celiac patients show a higher level of blood glutamine after gliadin feeding than do normal children. The glutamine appears to be in bound form. This has been confirmed by a number of observers,[43] although it has also been suggested that this effect may not be a specific indication of gluten-induced enteropathy but a more general result of small intestinal damage.[66] It might, of course, be a valuable diagnostic test for celiac disease, but it is generally regarded as not sufficiently reliable. It remains, however, a most interesting and suggestive observation. Peptides do appear to pass into the blood rather readily in these patients,[45, 67] but there is no satisfactory evidence to show that they are, in fact, the deleterious agent; they may be harmless concomitants.

Is there a genetic background? Several investigators[68, 69] have put forward suggestive evidence that celiac disease or related minor disabilities occur more frequently among relatives than can be accounted for by chance. A more extensive genetic study has been reported recently[70] which gives further support to the view that a significant proportion of the celiac patients who respond well to a gluten-free regimen might be expected to have a genetic fault. Further advance of knowledge on this aspect of the problem may depend upon more precise definition of the metabolic faults involved.

Aspects of the syndrome secondary to the enteropathy. The enteropathy probably accounts for the interference with and delay in absorption and the characteristics of the stools. It is possible some other factor—fat excretion according to some investigators—may also be concerned. Iron deficiency and in some cases a deficiency of calcium may be attributed to faulty absorption. Whether this also accounts for folic acid deficiency in some cases is unknown. The protuberant abdomen is presumably due to the intestinal dilatation and fermentative changes in the lumen. The wasting must be largely attributed to anorexia. The patient with a pancreatic enzyme deficiency has a greater absorptive defect, but may show little evidence of malnutrition; appetite in this group is usually good.[71] The loss of appetite might be a direct effect of the deleterious agent or it may be due to the enteropathy; anorexia returns promptly after the reintroduction of gluten into the diet of a celiac patient in remission. The combination of anorexia and intestinal inadequacy may, over a long period of time, lead to a wide range of nutritional deficiencies, usually of a minor character. Deficiencies of some members of the vitamin B complex may be due, at least in part, to competition between the intestinal flora and the host for common nutrients.[72]

Psychological effects. The peculiarly difficult and unhappy temperament of celiac children is well known to all who have been concerned with their care. It has been suggested that psychological factors play an important part in the cause of this group of disorders.[71, 73, 74] However, these personality difficulties are not a feature of patients with pancreatic enzyme deficiency. They seem to be characteristic of patients with gluten-induced enteropathy. When these children are placed on a gluten-free regimen, a striking change in temperament occurs and they become happy, cooperative, normal children. When gluten is reintroduced into the diet, difficulties in handling the children soon develop and

within a few days many of the temperamental features of the celiac child are again evident. It is not possible to decide at the moment whether this is secondary to the alimentary changes or whether it is a direct effect of wheat gluten in these individuals. It is certainly difficult to escape the conclusion that wheat gluten is the essential cause of these temperamental difficulties. While the psychological peculiarities of the celiac child do not help effective management, it is difficult to see on what grounds they can be regarded as playing an important part in the cause.

Daynes[75] has claimed that a wider range of behavioral difficulties may be associated with dietary wheat gluten. The main evidence is based on apparent improvement on a gluten-free diet. It must be stressed, however, that there is no evidence that the patients studied were suffering from any form of celiac disease, or should it be assumed that they were necessarily intolerant of gluten. As already pointed out, the establishment of a gluten-free regimen involves many changes besides exclusion of wheat-gluten. Dr. Daynes allowed us to study one of his patients, a child who had shown marked improvement in behavior on a gluten-free diet. Detailed studies of this boy revealed no evidence of celiac disease and the application of a blind test showed that he tolerated wheat-gluten in large doses without demonstrable effect. It would seem, therefore, that the observations reported by Daynes may not be related to the temperamental changes observed in celiac disease.

Growth effects. Growth is commonly depressed in celiac disease. This does not appear to be a feature of uncomplicated pancreatic enzyme deficiency, although of course, it may be seen in children with complications such as pulmonary lesions or infection. No doubt nutritional inadequacies, if present, must play some part in the growth defect, but there are reasons for doubting that this is the whole story. Sheldon[1, 2, 20] has carried out a great number of elegant studies on growth in celiac disease. He has shown that growth proceeds at a more rapid rate than normal in the celiac child on a gluten-free regimen. When gluten is reintroduced into the diet, growth is retarded. The change in rate of growth is remarkably dramatic. A patient has been described[45] in whom the growth defect was the dominant feature; the enteropathy was minimal. Establishment of a gluten-free regimen caused a dramatic increase in growth rate, which was evident before the level of fecal fat had altered significantly. Bone age is retarded, so that growth may continue well beyond the normal expected age limit. These observations on the effect of gluten on growth raise the question whether this effect is due to a direct action of the gluten, rather than to a secondary effect of nutritional disturbance. A final answer cannot be given at this time.

TREATMENT

The standard lines of treatment needed to deal with symptomatic deficiencies or intestinal infestation require no comment here. Some points with regard to the gluten-free regimen deserve further consideration.

How strict should the gluten-free regimen be? In our opinion, the aim should be complete elimination of all wheat or rye gluten from the diet.[18] Many observers have reported that small amounts of gluten can upset one of these patients once they have been on a gluten-free regimen. It may be that the recovery in the absorptive capacity of the intestines increases their sensitivity; a damaged mucosa and poor absorption are, to some extent, a protection against a dietary toxic agent. We have the definite impression that a strict dietary regimen has been successful in patients in whom less effective dietary control has failed previously. This is, however, a difficult point to prove, since, for obvious reasons, other forms of therapy are usually necessary in such patients.

What other foods should be permitted? Most observers agree that any other foods may be given and that there is no need to restrict intake of fat. Some care obviously should be exercised in the management of a severely ill child, but dietary restriction need

not extend beyond the ordinary bounds of prudence. It is most important that the children should receive sufficient calories. The possibility of sensitivity to other food materials, such as milk, should be borne in mind in a child that is not doing well on a gluten-free regimen; appropriate adjustments in the diet may be necessary.

Are other supplements necessary? Various measures, such as vitamin B therapy,[76, 77] have been used in the past. The impression from recent studies is that they are only required when deficiencies are evident. Care should obviously be taken to ensure that the diet contains an adequate supply of iron, calcium, vitamins and other essential nutrients; if it should prove to be defective, modification or supplementation is necessary.

What are the best criteria for assessing the results of therapy? These children usually show striking clinical improvement, but it is not so much the initial improvement that is important in relation to therapy as whether recovery is complete or only partial. The significance of this point is clearly indicated by the studies that have been made of former celiac patients who were generally regarded as being recovered from the disease.[23, 78] The premature abandonment of a gluten-free regimen may lead to all the trials of adult steatorrhea; on the other hand, the continuation of a severe dietary restriction for an indefinite period unnecessarily is equally undesirable.

It is clearly impractical to subject these patients to a complete assessment of intestinal and metabolic functions at frequent intervals. Such studies take at least 2 weeks to complete and one can hardly expect a patient, who may be enjoying new-found health for the first time, to submit to hospitalization for such a long time. Investigations that can be carried out on an outpatient basis or within a relatively short time are obviously needed. The gliadin test[65] clearly would be of great value in this way, but, unfortunately, there is not sufficient information on the correlation of this test with recovery; indeed, the abnormality may persist. It may be that this is an indication for continuing a gluten-free diet indefinitely, but such a conclusion cannot be reached on present evidence. Sheldon advocates growth measurements as a guide. These are difficult to assess in many patients, since a number of other factors may be involved. In our experience, the levels of fecal fat are the simplest and most reliable guide.[79] One must, of course, guard against "treating the stools and not the patient."[80] Nevertheless, there is ample scope for new and better methods of assessment.

How long should the gluten-free regimen be continued? It is clear that many patients with gluten-induced enteropathy may require a gluten-free regimen indefinitely. On the other hand, there is also evidence that many patients who benefit from a gluten-free regimen may be able to dispense with any dietary restriction later on. The points discussed in the previous section are highly relevant to this problem. It may also be of value to classify these patients more precisely on the basis of a definitive test as already described. As our knowledge of the details of pathogenesis becomes clearer, it is likely that better methods of assessment will become available and provide a more satisfactory answer to this question.

PROGNOSIS

The only aspect of prognosis that may be discussed usefully here is the future health of a child with the celiac syndrome who responds to a gluten-free regimen. From what has already been said, it is abundantly clear that premature return to a gluten-containing diet is highly undesirable. Anyone who studies adult patients with steatorrhea knows to what an extent chronic ill health and invalidism may result when a patient with continuing gluten-intolerance consumes an ordinary diet. It may well be that all children with the celiac syndrome who respond to a gluten-free regimen do not require this dietary restriction indefinitely. One cannot fail to be impressed, however, by the repeated statement made for many years that children with celiac disease recover at puberty or thereabouts; it

will be found in every one of the older text books. This has been shown to be untrue.[23, 78, 81] Mention must also be made of the tendency of former celiac patients to have repeated crises of a deficiency of folic acid. The reason for this remains obscure. The effective clarification of these problems would be of real service to the celiac patient.

It is a pleasure to express my thanks to Sir Wilfrid Sheldon and a number of my colleagues in Birmingham for helpful advice on the preparation of this paper.

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Torsion of the testicular appendages

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TORSION of the hydatid of Morgagni was first described by Ombredanne[1] in 1913. In 1922 Colt[2] defined torsion of the hydatid of Morgagni as a separate entity from the previously described torsion of the testicle. It was some time later that case histories began to appear in the American literature. In 1932 Foshee[3] summarized 46 cases including 2 of his own. Since then torsion of the testicular appendages has been reviewed in urologic publications,[4-10] but surprisingly little has appeared in pediatric literature. Recognition of the entity by pediatricians is important since the highest incidence occurs in the age group from 5 to 15 years. It is the purpose of this paper to establish an awareness of the clinical condition of torsion of the testicular appendages in those responsible for the care of children.

The hydatid of Morgagni is a vestigial structure found in two-thirds of adult males. Actually it is only one of several appendages that may be attached to the testicle. It is usually located in the groove between the globus major of the epididymis and the testicle, but may be situated on any part of the anterior surface of the upper pole of the testis. It varies from 2 to 15 mm. in length and may or may not be pedunculated. Microscopically the structure consists of loosely arranged connective tissue. Vascular spaces containing albuminous material and lined with endothelium were described by Vermeulen and Hagerty.[8] These had the appearance of lymph channels rather than epithelial-lined tubules. The surface of the hydatid is covered with columnar epithelium which becomes continuous with the flat epithelium of the tunica albuginea of the testicle. When the structure becomes twisted hemorrhage is found in the connective tissue and infiltration with polymorphonuclear leukocytes becomes a prominent feature.

Other appendages which may be found on or about the testicle and occasionally give rise to clinical symptoms include (1) the appendix of the epididymis which is a pear-shaped body attached to the globus major of the epididymis, (2) the vas aberrantia of Haller, usually found at the junction of the body and tail of the epididymis near the epididymotesticular groove and, (3) the organ of Giraldès or paradidymis which is actually attached to the anterior part of the lower end of the cord just above the globus major (Fig. 1).

The embryologic development of the hydatid of Morgagni is somewhat different from that of the other testicular appendages. In the young embryo, two duct systems are present. The Müllerian ducts are the female component and become the uterine tubes, uterus, and vagina of the female embryo. If the embryo becomes a male the mesonephric tubules connect with the gonad to form the duct system of the testicle. At the same time

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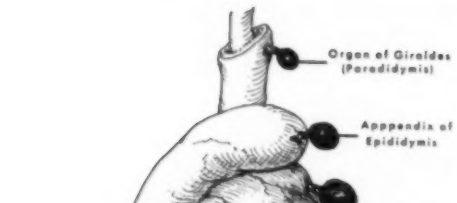

Fig. 1. Testicular appendages. (Illustration reproduced by permission of Dr. Meredith Campbell: Pediatric Urology, Philadelphia, 1951, W. B. Saunders Company, p. 549, Fig. 270.)

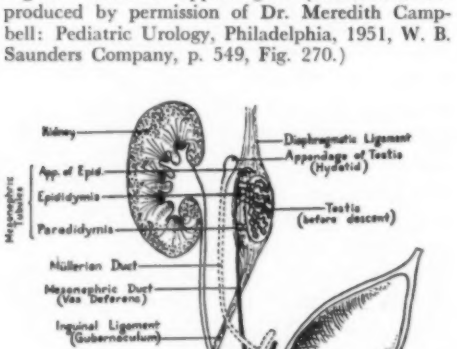

Fig. 2. Embryology of the genitourinary system. (Illustration reproduced by permission of Dr. Bradley M. Patten: Human Embryology, New York, 1946, Blakiston Company, p. 578, Fig. 361.)

the Müllerian ducts become rudimentary; however, the cephalic end may become attached to the upper pole of the testis to form the appendix of the testis or the hydatid of Morgagni. This, then, represents the vestigial fimbriated portion of the Fallopian tubes in the female. The mesonephric tubules, cephalad and caudad to those joining the testicle, form the appendix of the epididymis, vas aberrantia of Haller, and paradidymis (Fig. 2).

Several reports have been published describing vestigial structures on the broad ligament of females. Reis and DeCosta[11] have reported 5 such cases. The structure is usually oval, averaging about 8 mm. in diameter and often constricted in the center. It is usually single but may be multiple. Pedicles up to 12 cm. in length have been reported. These structures probably represent the cephalad portion of the mesonephric duct and therefore can be said to be the counterpart of the hydatid of Morgagni in the male. Torsion of this vestigial body in the female can produce symptoms of pain not unlike those found in torsion of the appendix of the testicle in the male.

The hydatid of Morgagni and the appendages of the epididymis and spermatic cord become important clinically when torsion occurs. Why these structures become twisted is not known; however, there are apparently several predisposing factors. A testicular appendage with little or no pedicle is not likely to undergo torsion. It has been suggested[3, 12] that the larger the appendage the more likely it is that twisting will occur, although torsion of pinhead-sized hydatids has been reported. Occasionally external trauma appears to be a factor, but more often there is no preceding history of injury. Randall[4] postulated that violent cremasteric contractions may play a part.

The cardinal symptom of torsion of the testicular appendages is pain in the testicle involved. It is usually quite sudden in onset and often radiates into the groin and back on the same side. In some cases the pain is mild and in others severe. Careful history will often reveal previous episodes of testicular discomfort of only a few minutes' duration. Four to 12 hours after the onset the pain often begins to subside. Gross[13] has suggested that this may follow destruction of the nerve reflex. Constitutional symptoms are usually lacking, although nausea and vomiting may occur. Fever is absent.

The child with sudden onset of pain in the testicle presents a problem in which early diagnosis is essential. If the patient with torsion of a testicular appendage is examined

early there may be only tenderness of the testicle. Cases have been noted in which the appendage was palpated as a hard mass at the upper pole of the testis. Within a few hours after the first symptoms appear, there is usually swelling of the scrotal contents on the involved side. This swelling is due to the accumulation of bloody fluid within the tunica vaginalis and not to the swelling of the testicle itself. Occasionally transillumination will differentiate testicular swelling from a hydrohematocele, but the opacity of the fluid often gives the impression that the scrotal content is a solid mass. This collection of fluid makes palpation of the twisted appendage difficult or impossible. Usually the swelling progresses for 24 to 48 hours.

Typically, scrotal edema and redness occur a few hours after the appearance of the hydrohematocele. McFadden[14] states that the early appearance of edema and redness of the scrotum occurs in only 2 conditions: (1) torsion of the testicle and (2) torsion of the testicular appendages. Walton[15] noted redness of the scrotum in some cases of epididymitis, but this was usually confined to the area overlying the epididymis. It can be said that generalized redness and swelling of the scrotum is at least highly suggestive of torsion of the testicle or one of its appendages.

Prehn[16] described a sign which has been of value in differentiating torsion of the testicle and its appendages from epididymitis. When the scrotal contents are elevated the pain of epididymitis is less intense. When torsion has occurred elevation of the scrotum fails to relieve the pain and often accentuates it.

Torsion of the testicular appendages and torsion of the testicle itself present almost identical clinical signs. It is generally agreed that the pain is usually more intense in torsion of the testicle, but this cannot be relied upon with certainty as a differential point. If the testicle is high in the scrotum it may be due to a twisting of the cord through several turns; however, torsion of a testicular appendage may result in a hyperactive cremasteric reflex which may retract the testicle into the inguinal canal. Most authors concede that it is difficult if not impossible to distinguish clinically between torsion of the testicle and torsion of one of its appendages. This fact determines to a large extent the approach to treatment.

Testicular pain secondary to trauma, to mumps orchitis, and to epididymitis must be considered in the differential diagnosis. The last may be the result of hematogenous spread of infection, but contiguous extension from the urethra and vas deferens occurs more commonly. Because of this mode of spread, tenderness may be elicited over the seminal vesicle on the affected side on rectal examination. At the onset, the spermatic cord and the globus minor of the epididymis are swollen and tender but later the entire epididymis becomes involved. The onset of pain is usually more insidious in epididymitis than in torsion of the testicle or its appendages and, as mentioned above, can be relieved by elevation of the scrotum. Chills and fever are often found in acute epididymitis.

Trauma which results in contusion of the testicle can usually be diagnosed by history.

Orchitis is uncommon in children except as a complication of mumps occurring after puberty. The pain of orchitis usually develops slowly and often precedes the swelling of the testicle by several hours. A history of parotid swelling, while helpful, is not essential in establishing the diagnosis of mumps, since the virus may affect only the testicular tissue.

Tumors of the testicle usually enlarge gradually and pain is a late symptom in contrast to the early development of pain and swelling in torsion of the testicle or of one of its appendages.

The treatment of torsion of a testicular appendage is surgical removal of the twisted structure.[17] Without surgical intervention the appendage becomes necrotic and sloughing occurs. The bloody fluid and necrotized tissue within the tunica vaginalis are eventually absorbed, but only after 2 to 3 weeks of painful swelling. Following early removal of a twisted testicular appendage, the scrotum and its contents are often completely normal within a week. It may be extremely difficult, clinically, to differentiate between torsion of

the testicular appendage and torsion of the testicle itself. Detorsion of a twisted testicle is most successful when performed early. It would seem that early operation on a child thought to have torsion of a testicular appendage would not only shorten the convalescense when the diagnosis is correct but at the same time preserve the integrity of the testicle if the twisting has occurred in the spermatic cord.

SUMMARY

The anatomy and embryologic development of the testicular appendages are reviewed. These structures become clinically important when torsion occurs. The symptoms are pain in the testicle, swelling of the scrotal contents, and redness and edema of the scrotum. Testicular pain secondary to trauma, to mumps orchitis, and to epididymitis must be considered in the differential diagnosis. Surgical removal of the twisted appendage is recommended.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor

Gordon F. Vawter, M.D., Assistant Editor

THIS was a 4-day-old white male, who was transferred from an outside hospital because of jaundice which he had had since he was 4 hours old.

The baby was born after a gestation of 9 months to a gravida III, para II, 23-year-old white woman. Throughout her entire pregnancy, no drugs were taken other than multivitamins. During pregnancy the mother gained 38½ pounds. Labor lasted for approximately 5 hours. The membranes ruptured spontaneously in the delivery room and the child cried spontaneously after birth. Icterus was noted shortly after birth, as indicated above. The obstetrician described the amniotic fluid as meconium-stained. The child's birth weight was 6 pounds, 5 ounces. He was breast fed during the first 2 days but seemed to be a poor feeder.

The urine was noted to contain bile; no bile was demonstrated in the stools. The jaundice increased steadily and the baby was transferred to this hospital.

There are 2 siblings. Both are girls, one 4 years of age, and one 2 years of age, and both are living and well. No jaundice was noted in these children after birth, nor were exchange transfusions required. The mother has never had a transfusion.

On admission, temperature was 99.2° F.; pulse, 164 per minute; respirations, 32 per minute and regular; blood pressure 50 mm. Hg, (flush); length, 49 cm.; and weight 5 pounds, 10 ounces. Head and chest circumferences were 33.5 cm. each. The infant appeared to be well developed, severely icteric, and acutely distressed. The icterus of the skin had a greenish tint. There were several petechiae over the body and head, and generalized edema. The head was normocephalic, with overriding sutures. The abdomen was soft, the liver was palpable 8 cm. and the spleen 3 cm. below the costal margin. The child appeared extremely irritable and had poor suck and grasp reflexes. The Moro response and muscle tone were poor. There was 4 plus "jitteriness."

Urinalysis showed no albumin, 3 plus bile and 15 red blood cells and 30 white blood cells per high-power field; the white blood cells showed toxic granules; no casts were seen. The initial hemoglobin was 9.1 Gm.; leukocyte count uncorrected was 72,000 per cubic millimeter; however, there were 300 nucleated red blood cells per 100 leukocytes. The baby's blood was type A, Rh positive. The Coombs test was 2 plus positive. The mother was type A, Rh positive. Initial

study of the baby's serum showed a direct bilirubin of 44.8 mg. per cent, and a total bilirubin of 81.1 mg. per cent. The mother's serum agglutinated all bloods tested by the indirect Coombs technique.

Because of the seriousness of the situation, it was felt that an exchange transfusion should be carried out using the least incompatible blood available. This was done. The initial venous pressure was 100 mm. blood; the hemoglobin, after exchange, was 11.5 Gm. per cent. At 91 hours of age, approximately 8 hours after the first exchange transfusion, the serum bilirubin was still 40 mg. per cent direct and 76 mg. per cent total, and another exchange transfusion was performed. At 99 hours of age, the serum bilirubin was 19.4 mg. per cent direct, 41.4 mg. per cent total. At 102 hours of age, a third exchange transfusion was performed. Hemoglobin always showed a rise in the postexchange specimen. The first 3 exchange transfusions were performed using Group A, Rh positive blood. During the fourth exchange transfusion the baby had some cardiac irregularities and for this exchange transfusion, which was necessitated by the high bilirubin levels, blood was obtained from the mother, the red blood cells being separated from the plasma and resuspended in normal AB plasma. The child was started and maintained on antibiotics, penicillin, and streptomycin throughout his entire stay in this hospital. Blood cultures were obtained from all exchange transfusion samples. *Streptococcus faecalis* was grown from blood after the first transfusion, and thereafter in all samples.

He voided 6 to 9 times a day throughout his hospitalization. His condition gradually deteriorated. He exhibited twitching movements, had a left-sided seizure, and died approximately 2½ days after admission.

DR. FRED H. ALLEN, JR.* I think I should explain that I have guessed who this patient is, especially in view of the serologic results mentioned.

*Dr. Allen is Assistant Clinical Professor of Pediatrics, Harvard Medical School, Associate Hematologist, The Children's Hospital Medical Center, and Associate Director of the Blood Grouping Laboratory, Boston, Mass.

This is a case of erythroblastosis fetalis. The mother's serum agglutinated all blood specimens tested, and it was tested against a good many. In the hospital, because of the seriousness of the situation, it was felt that an exchange transfusion should be carried out, using the most compatible blood available. Some of the specimens of blood tested did show stronger agglutination than others, and those that were agglutinated less strongly were the ones chosen for the exchange transfusion.

This was an unusual case of erythroblastosis fetalis in several respects. First of all, the antibody involved was an extremely rare one and posed problems in itself. I shall talk about the antibody later. From the clinical viewpoint, the baby certainly had typical erythroblastosis with jaundice, enlargement of the liver and spleen, anemia, marked erythroblastemia, edema, and petechiae. The large amount of direct bilirubin is distinctly unusual, especially at such an early age, and indicates several possibilities. A great deal of bilirubin was conjugated and, second, the baby seemed to be unable to excrete it very well, suggesting some interruption in the integrity of the bile ducts. Possibly this child had something seriously wrong with the liver, perhaps a severe necrosis. Bacteremia was confirmed 3 times, although I do not know quite what to say about it. I wonder if it was related, perhaps, to the trouble with the liver. I assume that the baby had kernicterus. The symptoms were atypical, at least as far as this record goes. Opisthotonus is not described and this is a most characteristic symptom in a baby with this diagnosis. The protocol does not describe the extensor rigidity of the arms with clenched, internally rotated fists which is such a characteristic reflex in babies with kernicterus and, finally, when the baby died there was no evidence of the pulmonary hemorrhage which so very often accompanies death from kernicterus. Nevertheless, with such a high bilirubin with definite central nervous system signs, poor muscle tone, poor reflexes, and extreme irritability and jitteriness, there is no room

for doubt that the baby had kernicterus. The bacteremia again might be considered with respect to the neurological signs, but I think they could all be explained by the kernicterus, in spite of the fact that the convulsions which were described as a terminal event are a rather unusual manifestation.

The pedigree of this family was worked out by John Burrington who was then a third year medical student, and who went to the small town where these people lived and collected blood samples for testing at the Blood Grouping Laboratory.

First, let me describe the blood factors which this baby had and which the mother did not have. They were both Rh positive. The mother was C-negative, c-negative, E-negative, e-negative, Hr_o-negative and f-negative, while the baby was c-positive, e-positive, and Hr_o-positive. The mother's serum had a high anti-e titer, and a lower titer (1:32) of anti-Hr_o. In Fig. 1, the baby is shown by the arrow. The mother is homozygous for a rare Rh gene (— — D — —), as are 2 cousins (also shown in black). The 2 grandparents are probably related, for common surnames were found in the 2 family trees. However, Mr. Burrington was unable to show the exact relation of the baby's parents. They were both born and brought up in the same town. They thought they were not related, but it seems that they were.

To describe the rarity of this Rh type, it is necessary to recall that the Rh factors C and c, E and e are allelic pairs. In the general population, 3 per cent of people are e-negative; all of these are E-positive; 27 per cent have both e and E, and 70 per cent lack E but have e. Thus, everyore has e or E. It is the same for factors C and c; 20 per cent are c-negative, C-positive, 50 per cent have c and C, and 30 per cent lack C but have c. Again, everyone has either c or C, or both.

The mother of this child had none of these factors—no e, E, c, or C. No person of this type has been found in tests of unselected people, so it is very rare, and this

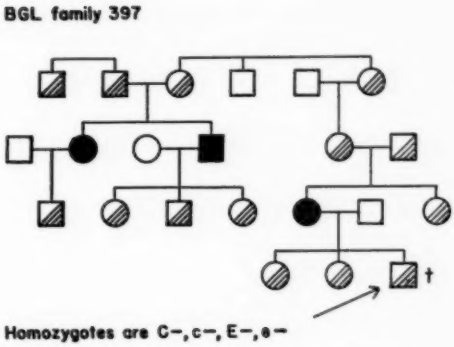

Fig. 1. Family pedigree. Black figures indicate homozygotes and hatched figure heterozygotes for the — — D — — gene.

alone indicates that the Rh groups are responsible for the clinical problem in this case.

The discovery of this rare Rh type was published in 1950 by Race, Sanger, and Selwyn[1] in England and since then 12 or more similar cases have been reported in various parts of the world. There are many allelic genes that control the inheritance of the growing list of Rh factors, but there are 8 so-called "primary" Rh genes. The gene in which we are interested today, and for which the mother was homozygous, is named $\overline{\overline{R}}^{o}$ or — — D — —. This gene produces all of the usual D factors (of which at least 5 are now known) but does not produce C, c, E, e, f, rh_i, or Hr_o. It does produce G. The failure to produce Hr_o is perhaps the most significant characteristic of this gene. In addition to the anti-e and anti-Hr_o that this woman had, there were other as yet unidentified antibodies, which I assume are Rh antibodies.

In summary, this was a case of erythroblastosis caused by a very rare combination of antibodies. Almost surely, there is complicating kernicterus, and possibly bacterial disease. Donors were very difficult to find. Actually, we did not know of any compatible donors within a radius of many hundreds of miles. There was a woman in South Hadley

who was of the same Rh type but she was group B and therefore incompatible.

Since there were no compatible donors known, could kernicterus have been prevented in this baby? Erythroblastosis should have been diagnosed very soon after birth because of the jaundice and the positive Coombs test. I think kernicterus could have been prevented by multiple exchange transfusions of incompatible blood, because we know that such transfusions do have a favorable effect on the jaundice, though a less favorable effect, we believe, than compatible blood. As far as the prognosis for possible future pregnancies is concerned here, if a subsequent baby is born alive, there are 3 compatible donors, the woman herself and her 2 cousins, who are available. A subsequent baby could certainly be saved, without neurological sequelae, by the use of prompt, and possibly repeated exchange transfusions. Whether a subsequent baby would be born alive at all is perhaps a problem. The anti-e has a high titer and the woman might very well have a stillbirth in her next pregnancy. Since this baby was born alive and in good condition, it is quite probable that a subsequent baby also would be born alive and in good condition.

DR. VAWTER. This baby was sent here with a diagnosis of biliary atresia, made on the basis of stool and urinary findings.

DR. ALLEN. In the past this was a fairly frequent occurrence, especially with babies about 2 to 3 weeks of age. Dr. Hsia[2] in 1952 analyzed the patients admitted with this diagnosis and found that 23 of 156 had erythroblastosis, and nothing wrong with their bile ducts.

DR. VAWTER. This baby received somewhat over a liter of blood at exchange transfusion. Does this represent a sufficient quantity of replacement to clear away the circulating antibodies?

DR. ALLEN. When one uses compatible blood at exchange transfusion and a pint of blood for the exchange, approximately 25 per cent of the antibodies come out. If one is trying to remove all the antibodies, he must do a great many exchange transfusions. This can be done, I suppose, if necessary. One thing might be said about incompatible blood—it undoubtedly does remove somewhat more antibodies than exchange transfusion using compatible blood, though that is not really an important aim in exchange transfusion therapy.

DR. SHERWIN KEVY. Dr. Goldblatt, did the child ever have opisthotonus or cardiac murmurs?

DR. GOLDBLATT. No.

DR. KEVY. Dr. Allen, in children who have such a high level of bilirubin, do you ever see renal damage, bile nephrosis, or perhaps tubular necrosis?

DR. ALLEN. I do not know that this has ever seemed to be of clinical importance.

DR. VAWTER. Does hemoglobinuria occur, or would you expect it in this patient?

DR. ALLEN. Hemoglobinemia in erythroblastosis occurs rarely, in very sick babies. I do not know whether, under such circumstances, hemoglobinuria occurs too, or whether the kidneys are damaged. Theoretically, the exchange transfusions of incompatible blood might have caused a hemolytic transfusion reaction, though this also is rare, as far as I know.

DR. VAWTER. The pathologic findings do not, of themselves, suggest that there were any peculiarities in the *erythroblastosis fetalis*, and the complicating *kernicterus* which were found at the time of autopsy. There were no overt evidences of sepsis in this child and postmortem bacterial cultures of the heart's blood and lung were sterile, but there was an aspirational pneumonitis. The child, at the time of autopsy, had also lost all visible evidence of edema, had no excess fluid in any body cavity, and no longer had evidence of active bleeding tendency, with the exception of some minor hemorrhages in the lung which certainly did not constitute what one ordinarily thinks of as the massive pulmonary hemorrhage which may complicate kernicterus.

The brain was 30 grams overweight and showed characteristic yellow staining in the hippocampus, basal ganglia, olivary nuclei, dentate nuclei of the cerebellum—in short,

places where one would expect to see it. Histologic evidence of neuronal necrosis and glial activation accompanying this pigment was much less striking than one might have expected on the basis of the prolonged bilirubinemia which this child had. We found no explanation for the unilateral nature of the child's neurological findings.

The kidney (Fig. 2) was of interest because of marked yellow-orange staining of the proximal tubules associated with tubular degeneration with desquamation and pyknosis. Special stains showed the pigment to be strongly positive for iron so that there was a marked degree of hemosiderosis in the proximal tubules. There are bile-stained casts in the tubules, endothelial cell response within glomeruli, and leakage of protein into the glomerular space. These are compatible with a *hemoglobinuric, or shock nephrosis.* As Dr. Allen has suggested, this type of lesion is rare, and its significance in such cases remains to be elucidated.

The spleen was twice normal weight and there was an excess hematopoiesis with rather young forms quite commonly seen. There was a hyperplasia of the splenic littoral or reticulum cells. The enlarged liver

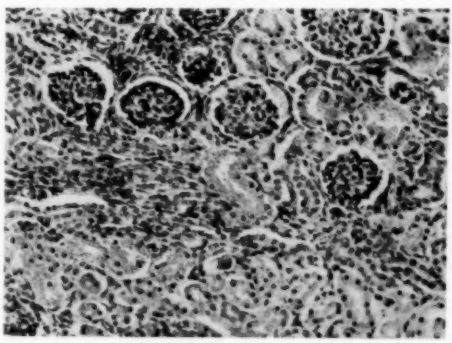

Fig. 2. Deep staining tubular cells with loss of nuclei (seen near the bottom of the photograph) indicating tubular degeneration. More conspicuous is the marked granularity of the cytoplasm of proximal convoluted tubular cells, indicating hemosiderosis. There is some leakage of protein from glomeruli which often appear ischemic. (Hematoxylin-eosin stain. × 325; reduced approximately ½.)

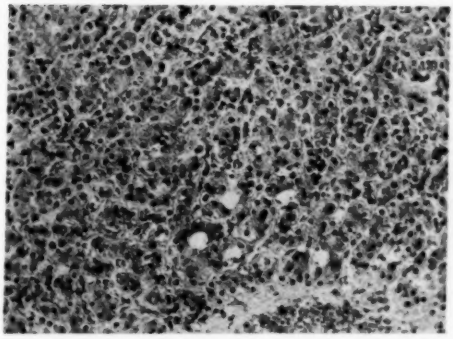

Fig. 3. Abnormal persistence of immature erythropoietic cells in hepatic sinuses is diagnostic of erythroblastosis. Continuity of hepatic cell cords is generally fairly well preserved. A number of bile plugs fill canaliculi, especially on the right of the photograph. (Hematoxylin-eosin stain. ×250; reduced approximately ½.)

(Fig. 3) contained no obvious lesion or necrosis to account for obstruction to bile flow although there were erythropoiesis, hemosiderosis, bile staining, and dense, heavy bile plugs, principally in the bile ducts and canaliculi. The patent external biliary system contained inspissated dark green bile and pasty white stool was found in the colon.

Dr. William Bradford, with Dr. John M. Craig, has done some very intriguing exploration in trying to assess and analyze the nature and character of the bile plugs which exist in the canaliculi of such livers. It is too early to say much more than that their results emphasize our ignorance of such a well-recognized finding. There are, however, suggestions of very significant peculiarities in solubilities in various polar and nonpolar solvents.

A PHYSICIAN. What can be done to help matters if one encounters a situation such as the one presented in this case?

DR. ALLEN. There are 2 things to do. First, one may type and cross-match brothers and sisters of the mother, who are the ones most likely to have a similar rare blood type. Cousins would be helpful, as they would have been in this family.

There is now a Registry of Rare Donors, sponsored by The American Association of Blood Banks and the Milwaukee Blood Center, 763 N. 18th Street, Milwaukee, Wisconsin, where one can get help in locating possible compatible donors. The mother, also, can always be used as a donor for her baby.

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COMMENTS ON CURRENT LITERATURE

Ocular findings in cystic fibrosis of the pancreas

CYSTIC fibrosis of the pancreas is now recognized as a hereditary disease of children, adolescents, and young adults, which results from a basic dysfunction of the exocrine glands. In its fully manifested form, this syndrome is characterized by pancreatic deficiency, abnormally high electrolyte content of the sweat, chronic pulmonary disease, and in some instances cirrhosis of the liver. The clinical manifestations are widely variable, since any or all of these aspects may be present to a more or less degree. While the nature of this generalized disturbance is not understood thoroughly as yet, the basic defect is thought to be hereditary, probably following in inheritance the distribution of a Mendelian recessive trait. Recent studies suggest that persons who are homozygotic for the trait tend to show the full clinical syndrome. Those whose inheritance is heterozygous with respect to this trait may exhibit little or no evidence of the disorder, may have as the only evidence an unusually high electrolyte level in the sweat, or may suffer from milder clinical manifestations of the disease. As high as 15 per cent of patients with cystic fibrosis are thought to have the disease expressed in partial form. Likewise, it has been estimated that from 20 to 30 per cent of the immediate relatives (both children and adults) of patients with cystic fibrosis of the pancreas will show sweat electrolyte levels which are elevated above the range considered normal. A smaller number of relatives may show some evidence of minor pulmonary involvement. Recent investigations have suggested that there is an association with basic allergy, and that some of the children with bronchial asthma, and perhaps some adults with chronic emphysema, may represent instances in which the trait responsible for fibrocystic pancreatic disease is of low penetrance genetically, and only partially expressed phenotypically.

Cystic fibrosis of the pancreas was recognized as early as 1936, when Fanconi and his co-workers[1] described 3 cases, pointing out the association between a cystic pancreatic fibrosis and certain well-defined changes in the pulmonary bronchial tree. However, the condition was not delineated as a separate disease entity until 1938 when 3 independent publications appeared within the year: Andersen,[2] Harper,[3] and Blackfan and May.[4] These studies presented clinical and pathologic findings, including observations made on material taken at necropsy in the 3 independent series of cases. The generalized and complex character of this disease syndrome was emphasized early, and clarification as to the nature of the condition has been the work of many investigators over a period of years, notably Andersen, Shwachman, Di Sant'Agnese, and their respective associates. Recent summary articles are informative and comprehensive.[5, 6]

In general, the diagnosis in cystic fibrosis of the pancreas has been made on the basis of the clinical findings and of 3 corroborative aids: the "sweat test" for detection of elevated electrolyte levels, chiefly the concentration of sodium chloride in the sweat, and a diminution of the trypsin content of duodenal fluid, together with roentgenographic evidence of chronic bronchopneumonia, emphysema, and microcardia. The protean character of the clinical manifestations has been re-emphasized recently by the publication of 2 preliminary reports concerned with ocular findings in cases of cystic fibrosis of the pancreas. The first of these reports by Bruce, Denning, and Spalter[7] appeared in the *Archives of Ophthalmology* for May, 1960. These authors first became "aware of complaints referable to impaired vision and abnormal fundus in patients with cystic fibrosis in the summer of 1958. Since that time, all patients admitted to the Babies Hospital with this diagnosis have had careful ophthalmological investigation. The present paper is a preliminary report of the eye findings in 24 patients."[7] In each of the 24 patients, definite diagnosis of cystic fibrosis of the pancreas was made on the basis of the clinical, laboratory, and roentgenographic findings. The majority of the patients in the series were known to have cystic fibrosis for some time before the abnormal eye condition was detected, and in every instance there had been evidence of progressive pulmonary disease from the time of the original diagnosis to the present admission. The chest was normal in only 3 of the 24 cases, as determined by x-ray examination at the time of the initial diagnosis. In the opinion of the authors, the patients with severe pulmonary involvement are the ones who tend to develop the abnormal ocular findings. Six of the group of 24 patients were classed as examples of "partially expressed" disease, these 6 showing pulmonary involvement which was characteristic, but having normal tryptic activity in the duodenal contents. However, as the authors state, many of these "partial disease" cases will develop the complete disease complex in time, and in some of these patients autopsy studies did reveal the characteristic pathologic features with typical pancreatic changes.

The eyes of all patients studied were dilated by means of 10 per cent Neo-Synephrine. Funduscopic examinations were performed independently by 2 opthalmologists. Ophthalmologic investigations included examination of the visual fields and refraction, whenever possible. Many detailed studies were carried out in an attempt to understand the ocular findings in these patients: analyses of serum electrolyte concentration, including pH determinations to evaluate carbon dioxide retention; total serum protein concentration, with separation of the albumin and globulin fractions; gamma globulin levels; sera screened for macroglobulins, prothrombin times, venous pressure studies, etc. Lumbar punctures were performed in order to measure spinal fluid pressure and gamma globulin concentration. In 8 patients serum vitamin A levels were obtained. Serum and spinal fluid levels of gamma globulin were elevated consistently.

A summary in tabular form of the significant eye findings for each patient is given by the authors. Because the patients were young and ill, certain of the indicated subjective tests, such as visual acuity and refraction tests, and mapping the visual fields could not be carried out fully or routinely in every case. Definite impairment of vision was noted in 4 of 10 patients tested in this respect. Characteristic findings in the ocular fundi comprised "varying degrees of venous engorgement and edema of the disc, marked in some instances by hemorrhages and in others by cystic changes in the macula."[7] Factors common to all 24 patients studied were severe pulmonary insufficiency, and elevation of gamma globulin content in the serum and in the spinal fluid. Six of 15 patients examined for venous pressure changes did have elevated venous pressure, and 3 of 10 patients tested with respect to cerebrospinal fluid pressure showed elevated

levels. In only 2 of the 24 patients in the series could any significant degree of carbon dioxide retention be detected. Seven of 18 patients had a prolonged prothrombin time. Normal amounts of macroglobulins were present in all serum specimens tested. The possibility that massive antibiotic therapy might play a role in the production of fundal changes in these patients is discussed by the authors; however, such an explanation is considered by them to be rather uncertain in view of the progressive changes observed.

Further observations on the ocular findings in cystic fibrosis of the pancreas were reported by Denning and Bruce[7] at the recent meeting of the Society for Pediatric Research: "Several aspects of the disturbed physiology in cystic fibrosis of the pancreas have been considered as possible causes of the eye changes—chronic hypoxia and hypercapnia, right heart failure, increased intracranial pressure, a bleeding tendency, or some disturbance of serum globulin."[8] However, investigations into these possibilities failed to disclose any specific abnormality that is constant and predictable. Investigations currently being continued by these authors include other physiologic studies and a study of the encephalographic findings in patients who show this disease complex in varying degrees of severity.

RUSSELL J. BLATTNER, M.D.

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Treatment of tuberculosis in children

A statement by the Committee on Tuberculosis and Respiratory Diseases in Children

ALTHOUGH extensive comparative studies on the use of chemotherapeutic agents in childhood tuberculosis have not been carried out on a randomized basis, as has been done with adults, the committee thinks that it is possible, on the basis of individual experiences and information derived from adult studies, to make certain recommendations.

USE OF DRUGS

Isoniazid. Isoniazid should be a part of every regimen for treatment of *active* tuberculosis. Although the usual dose of isoniazid for adults is 4 to 5 mg. per kilogram, doses as high as 30 mg. per kilogram per twenty-four hours have been used for children without complications. It is not certain that such large doses are required; a more usual level is about 15 mg. per kilogram daily taken in two or three doses.

A difference of opinion with respect to the proper dosage is due to the fact that in children, as in adults, a certain (at present unknown) proportion of patients rapidly inactivates the drug and renders it impotent by conjugation in the liver. To those who have used the larger doses of isoniazid, pyridoxine has not seemed to be a necessary additional drug for the prevention of neuritis in children, although it may be necessary in adolescents.

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PAS. Para-aminosalicylic acid is the most commonly used second drug when a combination regimen is employed. The dosage is usually 200 mg. per kilogram per twenty-four hours. When salts, sodium, potassium, or calcium para-aminosalicylate are used, the dose should be correspondingly larger, such as 300 mg. per kilogram daily. In general, children have a much better tolerance for all forms of PAS than do adults.

PAS apparently competes with isoniazid for conjugation by the liver and should be a part of the regimen when the dose of isoniazid is in the 4 to 5 mg. per kilogram range. The advantage of a double-drug regimen lies in the fact that the emergence of resistant strains of *M. tuberculosis,* which takes place during rapid multiplication of organisms, is delayed or prevented.

Streptomycin. Streptomycin is not used except under special conditions. The drug is undesirable because it must be administered intramuscularly and because it is toxic, especially to the eighth nerve. The usual dose is 20 mg. per kilogram per day.

Dihydrostreptomycin should not be used in pediatric practice, since it has a selective and often irreversible toxicity for the auditory division of the eighth nerve and since adequate audiometric studies may be impossible in the very young.

The newer antituberculosis drugs—such as viomycin, cycloserine, and pyrazinamide —usually have no place in the treatment of tuberculous children.

Triple-drug therapy. It has not been conclusively demonstrated that administration of isoniazid, PAS, and streptomycin simultaneously (so-called "triple-drug therapy") has a definite advantage over any two-drug combination that includes isoniazid, and it should be kept in mind that toxicity is increased proportionately. Therefore, "triple-drug therapy" should be reserved for the more serious forms of disease, as discussed below.

Corticosteroids. Corticosteroids should be used for the infant or young child who is dangerously ill in order to support him until antimicrobial drugs have an opportunity to produce some effect. Their routine use cannot be recommended at this time. The indications for the use of corticosteroids in pleurisy, meningitis, and endothoracic primary complex will be discussed below. The usual dose is 1 mg. per kilogram of prednisone per day for two to three months with gradual withdrawal.

DURATION OF THERAPY

The optimal duration of therapy is not known with precision, but the usual duration of drug therapy is at least one year and preferably eighteen or even twenty-four months, depending on the extent and severity of the disease, the longer duration being reserved for more serious forms of disease. When streptomycin is employed in a triple-drug regimen, it should be discontinued within a month after satisfactory clinical response.

TYPES OF DISEASE

Endothoracic primary tuberculous complex. Enlarged tracheobronchial lymph nodes and disease due to bronchial obstruction and/or bronchogenic spread are the most common forms of endothoracic tuberculosis in children. More extensive involvement may occasionally be seen. Drug therapy consisting of isoniazid and PAS should be continued for a minimum of one year. Roentgenographic findings may indicate that more prolonged therapy is necessary. Fresh pulmonary infiltrations respond quickly to drug therapy. Large mediastinal nodes and segmental involvement usually show slow changes. When endomural granuloma is the cause of obstruction, bronchoscopic removal of the granuloma may hasten the re-aeration of the segment involved. In young children with intense dyspnea caused by tuberculous bronchitis and tuberculous mediastinal nodes, marked relief may be obtained very quickly through the addition of corticosteroids.

TUBERCULOUS MENINGITIS

It is the opinion of the committee that all patients with tuberculous meningitis should receive triple-drug therapy, streptomycin being given daily (at least for a few weeks) and isoniazid in comparatively high dosage. Certainly the severely ill child, i.e., the child in coma or with suspected block, should be treated with corticosteroids; and some clinicians hold the view that all children with tuberculous meningitis should receive corticoids. There has not yet been sufficient controlled observation in children to permit the flat statement that all should receive corticosteroid therapy. The proper duration of therapy in cases of meningitis is unknown, but it would appear that treatment with isoniazid and PAS should be continued for a minimum of one year and in many cases longer, although streptomycin should be discontinued within a month after satisfactory clinical response.

MILIARY TUBERCULOSIS

Once again, triple therapy with fairly high doses of isoniazid and streptomycin is thought to be indicated during the first part of illness. Streptomycin may be discontinued after the temperature becomes normal. The patient should then continue on isoniazid and PAS for at least a year, although the optimal duration of therapy is unknown.

The corticosteroids may be used to assist in relieving extreme dyspnea associated with miliary disease.

EXTRATHORACIC TUBERCULOSIS

It is the opinion of this committee that all superficial and accessible abscesses caused by tubercle bacilli should be drained as freely and as readily as the abscesses caused by other organisms. Local excision of tuberculous tissue is perfectly safe provided the patient is receiving effective antituberculous chemotherapy.

Renal tuberculosis. The discovery of tubercle bacilli in culture of the urine, even though pyelograms reveal no evidence of deformity, calls for treatment in all cases. The reported evidence suggests that all but the very minimal cases of renal tuberculosis require a triple-drug regimen and that the duration of treatment should be two years.

Superficial lymphadenopathy. The general problems of drainage and excision are re-emphasized in cases of superficial lymphadenopathy. The preferred treatment is drug therapy, which may be followed by local excision. Some physicians prefer to aspirate pus and to administer corticosteroids as well as antimicrobial agents; others rely entirely on the antimicrobial drugs, principally isoniazid and PAS. Experience indicates that the duration of therapy should be at least twelve months.

Tonsillectomies and adenoidectomies are not performed routinely but should be considered on the basis of the individual problem.

Tuberculosis of bone and joint. The same principles of drug therapy and local excision and drainage enunciated above apply to these conditions. It is thought that in the non-weight-bearing structures immobilization is not necessary and may be detrimental. In the case of weight-bearing structures it is thought that the main problem is prevention of weight bearing and only now and then will prolonged immobilization be necessary. In the extremities, fusion should be avoided whenever possible.

Treatment always calls for isoniazid, usually associated with PAS. Some believe that triple-drug therapy should be used in bone and joint tuberculosis. Treatment should continue for eighteen to twenty-four months in all cases.

Serous effusions. All effusions should have diagnostic aspirations, and some clinicians advocate fairly complete aspiration of fluid. All patients with these manifestations of tuberculosis should receive a regimen containing isoniazid for a minimum of twelve months. Some physicians feel that the addition of steroids has some advantage in preventing pleural thickening and adhesions and particularly pericardial adhesions.

PULMONARY TUBERCULOSIS OF THE ADULT TYPE IN CHILDREN

Pulmonary tuberculosis in a child presents essentially the same problem as in adults. There is perhaps a higher incidence of this form of tuberculosis in pubertal and prepubertal girls. The same general principles regarding cavity closure and sputum "conversion" apply here as in adult tuberculosis, and the problems of the management of the open cavity are essentially the same. Thoracoplasty should by all means be avoided, although excisional surgery is often indicated.

SO-CALLED PROPHYLACTIC TREATMENT OF THE TUBERCULIN CONVERTER WITH NO MANIFEST DISEASE

If tuberculin conversion is known to have occurred within one year prior to the time of examination, it is the opinion of the majority of the committee that all children up to 14 years should be placed on treatment, using either one or two drugs, one of which should certainly be isoniazid. The treatment should be continued for at least one year and possibly longer. Isolation and bed rest are not necessary.

When the date of conversion of the tuberculin reaction is unknown and the patient has no signs or symptoms, it is thought that for maximal safety all patients less than thirty-six months* should be treated for at

*Of age. Ed.

least one year. Intercurrent infections, such as measles and pertussis, increase the hazard and therefore the need for antimicrobial therapy. It is also thought that the larger the initial tuberculin reaction the greater the risk of that child's developing active tuberculous disease.

Both recent converters and those whose conversion date is unknown should remain under careful observation for many years and should be closely followed in the event of intercurrent infections and as the patients approach the age of puberty.

Any tuberculin-positive child who is to receive steroid treatment for another disease should receive concurrent antituberculosis treatment.

A child with a positive tuberculin reaction should receive antituberculosis therapy for at least four weeks in the event of an attack of measles.

TUBERCULIN TESTING

The committee recommends that all children should be tested intradermally with a material equivalent to 5 TU of PPD-S. The first test under ordinary circumstances should be carried out at 6 to 8 months of age; if that test is negative, the test should be applied at least once a year thereafter, unless the child is known—or suspected—to have been exposed to tuberculosis.

In the event of known or suspected exposure to an open case of tuberculosis, a tuberculin test should be administered as soon as possible. If it is negative, it should be repeated as often as every four weeks until it becomes positive or until the longest possible period—three or four months—for the development of tuberculin allergy has passed. In the event that the contact with tuberculosis continues, the child should be tested as often as every month until contact ceases or until the tuberculin test converts. It is not yet certain whether the administration of isoniazid to an infant or young child who remains in constant contact with a case of tuberculosis, but whose tuberculin skin test is negative, will prevent infection or whether the drug merely suppresses infection and postpones the development of tuberculin sensitivity until drug administration is stopped.

JOHN S. CHAPMAN
KATHARINE H. K. HSU
EDNA M. JONES
EDWIN L. KENDIG, JR.
JOSEPH J. QUILLIGAN, JR.
HARRY SHWACHMAN
CLEMENT A. SMITH
MARGARET H. D. SMITH, *Chairman*

Books

The Child With Abdominal Pains.

John Apley, Springfield, 1959, Charles C Thomas, Publisher, 86 pages. Price $3.00.

This little monograph is a welcome and refreshing addition to the meager authoritative literature on this subject, particularly since the presentation is objective and backed by personally painstakingly collected statistics.

Recurrent abdominal pain is defined as abdominal pain, severe enough to affect activities, recurring on at least 3 occasions over a period longer than 3 months, and continuing in the year prior to the investigation. In the first section, detailed findings in school children, 108 of whom had recurrent abdominal pain and 312 of whom served as controls, are presented. An additional series of 100 consecutive children admitted to the hospital for abdominal pain is reviewed. Familial incidence, previous illnesses, age at onset, prognosis, and effect of treatment are reviewed.

The second section discusses etiology, the nature of the abdominal pain, and abdominal epilepsy. The book concludes with a chapter on management and treatment.

The author states in the preface that he "started with a bias toward organic causes . . . but the accumulating evidence gradually convinced me that in most cases an organic cause cannot be found." It is noteworthy that in treatment, appendectomy and exploratory laparotomy are not mentioned.

Every physician or surgeon seeing children will find an evening with the monograph a worthwhile investment of his time.

WILLIAM K. SIEBER, M.D.

The Placenta and Fetal Membranes.

Claude A. Villee, editor, Baltimore, 1960, Williams & Wilkins Company, 404 pages. Price $10.00.

This unique book was not intended for most pediatricians, obstetricians, or general practitioners. It is a compilation of the work of many investigators concerned with the structure and function of the placenta. It does not present the ABC's of this material for mere beginners but assumes that the reader is already thoroughly familiar with the basic principles of the subject including many finer points not only of anatomy but also of physiology and chemistry. It is rather a review of recent research put down to draw attention to questions still unsolved and to programs for future investigation.

The book is divided into 4 parts. The first is a series of 8 chapters dealing with specific subjects, each written by a different author or authors and each accompanied by an excellent set of references. A few of these are "The Placenta as the Fetal Lung," "Transmission of Antibodies From Mother to Fetus," and "Pathological Aspects."

The second part is the presentation of a Conference held in November, 1958, at Princeton, New Jersey, devoted to a "full discussion of current placenta research" and of "research needs for the future." Among the 35 participants are many of the authors of the monographs on abdominal pain. Much of what is present is highly technical and is concerned with subjects such as "the transfer of phosphate across the placenta," "steroid content of the placenta," and "oxygen gradients across the placentas of sheep and llama."

Some of the subjects such as "the source of amniotic fluid" and "transmission of viruses across the placenta" are less esoteric and more readily comprehended by the nonplacentologist. They are most interesting indeed.

The third portion of the book is a "Survey of the Literature." It is divided into sections dealing with such broad subjects as Endocrinology, Biochemistry, and Nutrition. Each of these is in turn broken down into subsections; thus, under Endocrinology there appear Androgens, Progestins, Relaxin, etc. Each subsection is arranged alphabetically according to authors, giving then the title of the work, the reference, and a brief summary of the conclusions established. This is an excellent collection and should be very helpful to anyone seeking information about recent work in the field.

The fourth and last part of the book is a list

of 8 American and 19 foreign investigators, giving the title and position of the individual, the names of his associates, and a brief summary of the problem presently being worked upon by that group.

This is a work prepared by a number of highly specialized investigators presenting their observations and conclusions concerning the placenta. It should be an invaluable and irreplaceable aid to persons currently working in the field of placentology but would be of limited value to the practicing physician.

MARIE B. VALDES-DAPENA, M.D.

Pediatric Anesthesiology, ed. 2.

M. Digby Leigh, M.D., and M. Kathleen Belton, M.D., New York, 1960, The Macmillan Company, 461 pages. Price $12.00.

This is the second edition of a well-known text on pediatric anesthesia. The new edition is entirely revised in both content and format, which vastly increases its informativeness and usefulness.

As the dust cover suggests, the book is essentially divided into 4 sections. Part I is concerned with the preanesthetic evaluation of the infant and child. It contains short descriptions of medical, surgical, and metabolic diseases and syndromes, stressing how each might affect the management of the anesthesia for such a patient. This section in itself is a miniature textbook of pediatrics.

Part II describes anesthetic agents, techniques, and equipment especially for children and evaluates in general aspects the respective advantages and disadvantages of each.

In Part III the authors discuss how they personally prefer to manage preanesthetic medication, preparation, and control of the infant and child during the operative and postoperative periods.

In Part IV the authors continue the discussion of their preferences in the anesthetic management for specific types of surgical procedures. In this last section the authors disclose many gems and "pearls of wisdom" they have gleaned in their many years of experience anesthetizing their little patients.

The book is written interestingly and its easily readable style makes its wealth of information readily available. This text is highly recommended for all those concerned with the welfare of children during anesthesia and operation.

JACOB B. FRIEDMANN, M.D.

Diuresis and Diuretics, An International Symposium.

E. Buchborn and K. D. Bock, editors, Berlin, 1959, Springer-Verlag, 382 pages.

This book is the result of a symposium held in June, 1959, concerning the theoretical and practical implications of diuretics. The authors and discussants are all well recognized as authorities in this field. Of the 17 papers presented only 4 are in English. The remainder are in German. The discussions following the presentations consist of questions in English and replies in German and vice versa. Although the subject matter is of great interest and is presented clearly, the intermixing of the 2 languages should prove to be too much of a handicap for the average reader. One can only hope that a complete English translation will be forthcoming.

DANIEL S. FLEISHER, M.D.

News and notes

The Institutes for Physicians and Nurses in the Care of Premature Infants at the New York Hospital–Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, are scheduled for Sept. 19 and Nov. 28, 1960, and Jan. 23, March 13, and May 8, 1961. Designed for physicians and nurses in charge of hospital premature nurseries and special premature centers and for medical and nursing directors and consultants in state and local programs for premature infants, the program is 2 weeks for physicians and 4 weeks for nurses. Attendance at each institute is limited to 6 physician-nurse teams. Participants pay no tuition fee and stipends are provided to help cover expenses during attendance. Early application is essential since plans are contingent on the number of applications received.

For further information write to Box 143, Institute in the Care of Premature Infants, the New York Hospital, 525 East 68th Street, New York 21, N. Y.

At its May meeting **The Society for Pediatric Research** elected the following officers: Gilbert B. Forbes, Rochester, president; Barton Childs, Baltimore, vice-president; and Clark D. West, Cincinnati, secretary-treasurer. Elected as members of Council were David Gitlin, Boston, 1961 to 1963; Sydney Segal, Vancouver, 1961 to 1963; Edna Sobel, New York City, 1961 to 1962; Forrest Adams, Los Angeles, 1961 to 1962; Irving Schulman, Chicago, 1961; and Alfred Bongiovanni, Philadelphia, 1961.

The following were elected to membership in the Society: Mary Ellen Avery, Johns Hopkins; G. N. Donnell, University of Southern California; D. Carleton Gajdusek, National Institutes of Health; J. H. Githens, Colorado; M. Green, Indiana; Robert E. Greenberg, Karolinska Institute; G. D. Hammond, University of Southern California; H. S. Harned, Jr., North Carolina; Felix P. Heald, Georgetown; S. L. Katz, Harvard; S. L. Leiken, Children's Hospital of District of Columbia; M. Lending, New York Medical College; Leonard M. Linde, University of California at Los Angeles; Chien Liu, Kansas.

A. E. Lorincz, Gainesville; Alvin M. Mauer, Cincinnati; W. J. Mellman, Pennsylvania; R. A. Miller, Northwestern; D. O'Brien, Colorado; Gerard B. Odell, Johns Hopkins; Thomas K. Oliver, Ohio State; E. P. Paulsen, Albert Einstein; Donald Pinkel, Roswell Park; Harris D. Riley, Jr., Oklahoma; I. M. Rosenthal, Illinois; J. D. Smith, Pennsylvania; J. M. Sutherland, Cincinnati; Jo Anne Whitaker, Southwestern; C. F. Whitten, Wayne; Sumner J. Yaffe, Stanford; and Alvin Zipursky, University of Manitoba.

The 1961 meeting of the Society for Pediatric Research will be held May 4 and 5 at The Traymore, Atlantic City, N. J.

The Midwest Society for Pediatric Research will hold its second annual meeting Nov. 2 and 3 in Milwaukee. Abstracts of papers to be considered for the program should be sent to the secretary of the society, Dr. William B. Weil, Jr., Department of Pediatrics, Western Reserve University, Cleveland 6, Ohio. Abstracts should be limited to 250 words and should be submitted in triplicate.

For further information address correspondence to Dr. J. C. Peterson, Milwaukee Children's Hospital, 721 North Seventeenth Street, Milwaukee 3, Wis.

The American Pediatric Society at its annual meeting at Swampscott, Mass., May 5 and 6 elected as officers: L. Emmett Holt, Jr., president; Edward B. Shaw, vice-president; Conrad M. Riley, secretary-treasurer; Robert J. McKay, recorder (editor); and Warren E. Wheeler, member of Council (for 7 years).

The following active members were elected: J. Edmund Bradley, Baltimore; Philip L. Calcagno, Buffalo; Charles D. Cook, Boston; Joseph Dancis, New York City; Lewis M. Fraad, New York City; James L. Gamble, Jr., Baltimore;

Andrew D. Hunt, Jr., Palo Alto; Norman Kretchmer, Palo Alto; Jonathan T. Lanman, Brooklyn; Irving Schulman, Chicago; Nathan J. Smith, Madison; Selma E. Snyderman, New York City; Edna H. Sobel, New York City; Judson J. Van Wyk, Chapel Hill; and Calvin W. Woodruff, Nashville.

The 1961 meeting of the American Pediatric Society will be held at The Traymore, Atlantic City, N. J., May 2 and 3.

"Newer Concepts of Growth and Development: Implications in Child Health" will be the subject of an institute conducted by the Schools of Public Health of the University of Michigan and the University of Minnesota to be held Nov. 28 to Dec. 2 in Minneapolis. It is jointly sponsored by the State MCH and CC Agencies of Michigan and Minnesota and financed by a grant from the United States Children's Bureau.

Each person selected by a state will have his travel expenses, tuition, lodging, and meals provided. Payment for expenses will be made by the University of Minnesota School of Public Health from funds provided by the Children's Bureau.

For further information contact Center for Continuation Study of the General Extension Division, University of Minnesota, Minn.

Dr. John Lind, Stockholm, is the foreign lecturer of THE JOURNAL OF PEDIATRICS Educational Foundation for 1960. His lecture schedule is as follows: Montreal, McGill University, week of Oct. 3; Burlington, University of Vermont, week of Oct. 10; Buffalo, University of Buffalo, week of Oct. 17; Nashville, Vanderbilt University, Oct. 22; Augusta, Medical College of Georgia, week of Oct. 24; and New York City, Albert Einstein College of Medicine, week of Oct. 31.

The American Board of Pediatrics, Inc., certified the following diplomates at Boston, Mass., on April 29 and 30, and May 1 and 2, 1960:

Agustsson, Magnus H., 11106 Mandel Avenue, Westchester, Illinois

Barr, Richard George, 1410 Upland Street, Chester, Pennsylvania

Benis, Max, 5655 Babbit Avenue, Encino, California

Berg, Robert Benjamin, 300 Longwood Avenue, Boston 15, Massachusetts

Bilzens, Valija S., 1214 58th Avenue, Southeast, Washington 27, D. C.

Bornstein, Harold D., Jr., 30 Washington Avenue, North Haven, Connecticut

Brodie, Hugh Russell, 2300 Tupper Street, Montreal 25, Quebec, Canada

Butler, John Kenneth, 144 South Harrison Street, East Orange, New Jersey

Chang, Sophia Ho-Ying Chien, 1755 East 55th Street, Brooklyn 34, New York

Coggeshall, Bayard, 20 Franklin Street, Morristown, New Jersey

Deane, Philip G., 3003 81st, Southeast, Mercer Island, Washington

Dobbs, June M., St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Dolan, Thomas Francis, Jr., Eastern Memorial Hospital, Ellsworth, Maine

Doray, Bernard H., 10980 Pasteur, Montreal 12, Canada

Eberly, Francis William, Children's Psychiatric Service, Harriet Lane Home, The Johns Hopkins Hospital, Baltimore 5, Maryland

Ellison, Alfred, Jr., 306 Green Avenue, Bay City, Michigan

Friedman, Gerald D., 400 Liberty Avenue, El Cerrito, California

Fuhr, Neal William, 2700 Sheridan Drive, Tonawanda, New York

Geldrich, John, 5932 Clayton Avenue, Baltimore 6, Maryland

Giesel, Roger Gresham, 3417 Custer Street, Cincinnati 8, Ohio

Gottlieb, Ruth Panzer, 110 Overbrook Parkway, Philadelphia 31, Pennnsylvania

Graves, William Horace, III, 3415 Edgewood, Ann Arbor, Michigan

Guntheroth, Warren G., 8903 27th Street, Northeast, Seattle 5, Washington

Hauck, Anna J., 300 Longwood Avenue, Boston 15, Massachusetts

Igo, Robert P., 4875 Terrace Drive, Seattle 5, Washington

Lacey, Hamer, 33 Pleasant Street, Gloucester, Massachusetts

Lauer, Ronald Martin, Apt. 515, Centurion Apts., 433 Jarvis Street, Toronto, Ontario, Canada

Lawrence, Ruth Anderson, 902 Landing Road, North, Rochester 10, New York

McCaul, Kevin F., 46 Van Buren Avenue, Norwalk, Connecticut
Michael, Alfred F., Jr., Children's Hospital, Elland and Bethesda Streets, Cincinnati 29, Ohio
Miller, John F., 723 Phillips Avenue, Toledo 12, Ohio
Paulsen, Elsa Proehl, 430 West 116th Street, New York 27, New York
Pollack, June Rae, 7000 Selkirk Drive, Bethesda 14, Maryland
Roberts, Arthur Renfrew, 501 South Brookhurst, Fullerton, California
Sanders, Lester Whitlock, Jr., 8323 Firshade Terrace, Cincinnati 39, Ohio
Scheiner, Albert P., 232 Varinna Drive, Rochester 18, New York
Schneider-Lerner, Hedi Ruth, 8001 South Yates Avenue, Chicago 17, Illinois
Schraeder, Gene Norman, 211 South Franklin Avenue, Pleasantville, New Jersey
Schrom, Herta Maria, 280 West Walnut Lane, Philadelphia 44, Pennsylvania
Selby, Gordon William, 1705 Chilver, Windsor, Ontario, Canada
Shanahan, Edward James, 1146 Clinton Avenue, Irvington 11, New Jersey
Sheridan, Sylvester Robert, 28 Cherry Hill Circle, Branford, Connecticut
Stephens, Martha, 33-52 85th Street, Jackson Heights 72, New York
Teitel, Maurice, 54 Sandy Hollow Road, Port Washington, New York
Thamarus, Warren Edward, Jr., 266 Highlake Road, Ann Arbor, Michigan
Tristan, Michael Peter, Boston Post Road, Sudbury, Massachusetts
Tyndall, Alice Dolores, 127 Maple Avenue, Red Bank, New Jersey
Warner, John Roger D., 1353 George Urban, Buffalo 25, New York
Watson, Richard Hardie, 47 Lincoln Street, Melrose 76, Massachusetts
Williams, Kenneth Owen, 1525 State Street, Santa Barbara, California
Winslow, Francis Edward, Jr., 213 51st Street, Virginia Beach, Virginia
Wolf, Stephen Harding, 32 Cloister Road, Levittown, Pennsylvania
Yaffe, Sumner J., Department of Pediatrics, Stanford Medical Center, Palo Alto, California
Yarus, Stanley S., 332 North 7th Street, Allentown, Pennsylvania

Special Foreign Certificates:
Ghadimi, Hossein K., Iran
Sanchez, Yolanda E., 2317 (Int 405) S. del Rosario, Gagalangin, Manila, Philippines
Sarioglu, Ali Riza, Turkey
Lee, Soo Hwa, Korea

The American Board of Pediatrics, Inc., subspecialty of pediatric Allergy, certified the following diplomates at Chicago, Illinois, on May 7 and 8, 1960:
Bailit, Irving William, 1233 Highland Avenue, Needham, Massachusetts
Bean, George William, 715 Fifth Avenue, Fort Worth, Texas
Boyden, Mary S., Medical Arts Center, 4th and Maine, Lawrence, Kansas
Brem, Jacob, 796 Pleasant Street, Worcester, Massachusetts
Dacanay, Eleonora P., Allergy Clinic, The Johns Hopkins Hospital, Baltimore 5, Maryland
Frick, Oscar Lionel, Department of Pediatrics, University of California Medical Center, San Francisco 22, California
Ghory, Joseph E., 2546 Auburn Avenue, Cincinnati 19, Ohio
Goldstein, David Myer, 416 North Bedford Drive, Beverly Hills, California
Gordon, Vida Hildreth, 2616 Kavanaugh Boulevard, Little Rock, Arkansas
Greenberg, William B., 90 Oak Avenue, Metuchen, New Jersey
Heimlich, Ernest M., Department of Pediatrics, UCLA Medical Center, Los Angeles 24, California
Johnson, Benjamin Allen, 1707 San Marco, Jacksonville 7, Florida
Kamin, Peter B., Children's Hospital of D. C., Washington, D. C.
Lidd, David, 1693 Skyline Drive, Pittsburgh, Pennsylvania
Mansmann, Herbert C., Jr., 206 Church Lane, Pittsburgh 38, Pennsylvania
Minden, Perc, 4849 Van Nuys Boulevard, Sherman Oaks, California
Rabinowitz, Haskell I., 1725 Orrington Street, Apt. 632, Evanston, Illinois
Rhyne, Marie Britt, Department of Pediatrics, Johns Hopkins Hospital, Baltimore 5, Maryland
Sellars, William Arnold, 238 West Tenth, Dallas 8, Texas

Vaughan, Victor C., III, Medical College of Georgia, Augusta, Georgia

The **American Academy of Pediatrics** announces the first two of the Postgraduate Courses it is sponsoring from July, 1960, to July, 1961. The first course, Pediatric Endocrinology and Genetics, will be given by the State University of New York at the Upstate Medical Center (Syracuse) under the direction of Dr. Lytt Gardner, November 9 to 11. The second course, Psychological Aspects of Pediatrics, will be given at the Yale University School of Medicine under the direction of Dr. Milton Senn, November 28 to 30.

Tuition for these courses is $40 for Academy Fellows and $60 for nonmembers. Registration is limited. For registration information write to the American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, Illinois.

A postgraduate seminar on **"Advances in Pediatric Therapy"** will be held at the Roosevelt Hotel, New Orleans, Sept. 23 under the sponsorship of the Louisiana Chapters of the American Academy of Pediatrics and the American Academy of General Practice.

Guest speakers will be Dr. Edward C. Curnen, Dr. Robert Denton, Dr. Alex J. Steigman, Dr. Milton H. Erickson, Dr. C. Everett Koop, Dr. Maxwell Finland, and Dr. Robert B. Lawson.

For further information contact Dr. G. J. Fruthaler, 3503 Prytania Street, New Orleans 15, La.

Correspondence

To the Editor:

Professor Bo R.* Nudnik, M.D., F.S.A.P.,** has been good enough to send me the substance of his recent address to the Lower Slobbovian Academy of Pediatrics. The subject of his paper was "Infant Feeding in Lower Slobbovia" and I have his kind permission to reproduce it in the pages of this JOURNAL.†

One thing about Dogpatch: its infants are breast fed.[1] Scantily clad, if at all, the bare-bottomed babies would appear quite incongruous with Heave-and-flo bottles in their mouths.

The same does not apply to Lower Slobbovia, or for that matter to Upper Slobbovia, or indeed to any part of the Slobbovian-speaking world. Infant feeding practices differ to some extent in the eastern region—that is, **Upper Slobbovia**—from those of the western region, Lower Slobbovia, and this is understandable considering that they are widely separated by the Atfrantic River.[2]

It is necessary to make some initial remarks on the development of infant feeding practices before proceeding to evaluate the present status of the artificial feeding of babies in Lower Slobbovia.

Historical development. At the turn of the century, Continental physicians gave immense impetus to an understanding of the mathematical basis of infant nutrition.[3] Numerous milk modifications came into being, some of them proving very popular in Lower Slobbovia.[4] Concurrently stool-gazing,[5] and divination by stool became virtually a subspecialty (clinical coprology), and formulas were adjusted for the baby according to the interpretation of the stool-gazers and clinical soothsayers.

Despite Jack Obi's plaint that "You cannot bring up a baby by mathematics," Roach of Lower Slobbovia did just that. His algebraic concoctions of milk were supplanted by the efforts of Gersten Berger in Lower Slobbovia, and of Ruby Tring in New Sealand. In 1910 the former managed to "humanize" cow's milk, at least superficially. He set out to compound SNA—to be like breast milk in every respect, and he succeeded—not in humanizing cow's milk as he had intended, but in producing a clean, safe, sterile milk for babies.

*For nothing.

**Fellow of the (Lower) Slobbovian Academy of Pediatrics.

†With apologies to Al Capp, cartoonist-creator of Li'l Abner within whose hallowed pages the realm of Lower Slobbovia is featured.

Ruby Tring, fiercely crusading on behalf of his esoteric system, found it necessary to supply ready reckoners to assist the mothers and doctors who undertook the hazardous task of the artificial feeding of infants. Unlike Gersten Berger's product, his "humanized" milk was a failure; somehow he never managed to get the synthetic fat to mix with the rest of the formula, and it had to be given separately by spoon.

Subsequently, formulas derived from evaporated milk became popular and with further burgeoning of research in nutrition, especially in Lower Slobbovia, much less consideration was given to matters like fat dyspepsia, the diagnostic criteria for which were so nebulous: "Those who frequently diagnosed fat intolerance saw many cases; those who never diagnosed it saw none."[6]

Milks unlimited. The effect of the numerous conflicting views on the nutritional requirements of infants resulted in a profusion of patent milks. SNA continued to lead the field and was exported to other parts of the Slobbovian-speaking world, where its novelty, Lower Slobbovian origin, attractively labeled tins, and high price induced numbers of physicians and mothers to rear their infants on its vaunted powder.[7] It traded on the fear of fat intolerance, presumably to be circumvented by its conglomeration of vegetable oils which had been substituted for the milk cream.

Simulac also made progress, urging its claim to simulate breast milk. The occasional megaloblastic anemia, following its use, like the occasional convulsion following liquid SNA feeding, was disconcerting but rapidly forgotten. Latterly Simulac has had extra iron added. Oilac entered the clinical scene with the usual attribute of a low fat content; not only that, but it established the tradition of "lac" as a suffix for "fixed" milks. The manufacturers of Lactem unsportingly used it as a prefix. The advent of the oddly named Drycow had little to recommend it aside from its deficient content of cream. Its principal virtue is that it is derived from contented cows. Paskudnik[8] comments: "It is a matter of some surprise that in this day and age these happy beasts have not yet produced a Tranquilac; even a mere coliclac, a laxlac, and certainly a broad-spectrum Optimolac would be useful for the gastric approach to paediatrics and valuable additions to our nutritional armamentarium."

Later research has highlighted the role of saturated fat[9] in infant nutrition, as well as the role

of protein and of electrolyte in the genesis of hyperosmolarity. As a consequence, saturated fats, osmolar loads, and protein- based calories have become such disturbing factors to the milk makers that a new rash of "fixed" milks have climbed on the bandwagon that trumpets "low in everything" (but price). Breastmil is rolling along smoothly behind SNA. Largely unknown as yet is Unfamil, allegedly nearest to mother's milk; what with its low renal solute load, no butterfat, and a desirable ratio of saturated to unsaturated fatty acids, it is clearly destined for big things; so is Caramel, whose manufacturers, Raker's, considering all contingencies, have wisely also issued a minimally altered Raker's Modified Milk. Then there is Muddylac, also prudently on the fence, with a protein content between that of breast milk and cow's milk; but, of course, corn oil replaces the saturated fats of the cream. The producers of Carnilac evidently don't care a fig for protein or fat and haven't tampered with either; the makers of Hiya-pro take the view that "protein" indicates exactly what it means: of first importance. They have not stinted it, though the cream has been reduced.

Laymener-Galem[10] points out that as much mathematics is involved in the above-mentioned milks as in those devised a half-century ago by Roach, Ruby Tring, and others. "These individuals are a process; the milks are a *fait accompli*. The mathematics, the slide rules, remain hidden within the tins. Like so much today, the mathematics is supplied precooked."

It is debatable whether the current profusion of modified and mutilated milks in Lower Slobbovia is any more "scientific" than the coterie of similarly savaged milks prevalent on the continent a half-century ago: Swiss milk, Biedert's cream, Gaertner's milk, van Durgern's renneted milk, Szekely's milk, Mortis' whey milk, Vigier's humanized milk, Lehndorf and Zak's dialized milk, Feer's milk, Schloss' milk, and all the rest. "Of making many milks there is no end."[11]

Eastern trends. Upper Slobbovia has been reasonably free of the flood of western milks, although one commercial concern has felt it necessary to produce no less than 16 varieties of milk, presumably all of them having a precise contribution to infant nutrition. Cow & Grate grinds out the following sparkling array: Full cream milk, Half cream milk, Special half cream milk, Separated milk, Tropical milk, Humanized milk, Hemolac, Lacidac, Modified Lacidac, Allergilac, Beurlac, Brestol, Peptilac, Sprulac, Frailac, and Prenatalac.

Paskudnik[8] terms these "an adventurous, if not reckless, and utterly un–Upper Slobbovian abomination." He continues, "If Frailac be necessary, why not Robustolac? Why Hemolac when one can give iron and iron-containing foods by mouth? What is the excuse for Sprulac? What possible advantages can Modified Lacidac have over the regular variety, and what can be so special about Special half cream milk? What is the case against Postnatalac?

"The use of a 'Tropilac,' a milk modified (low fat) for tropical use, has no physiologic foundation, and it would be wiser if Tropical Cow & Grate made a dignified exit from the clinical field. If a case can be made out for a Tropilac, then an equally good one can be adduced for milk modifications on a different geographical basis. Babies in the Slobbovian-speaking world could thrive on routine 'Lac,' while those in the Far East would do rather better on 'Yellac,' and what could be more suitable for Africa than 'Blac'?"

Conclusion. "There is no question" writes Laimpatz,[12] "but that the masses of milks are marketed as a treatment in search of a disease. In this respect they are doomed to failure. Wasted as well are all efforts to duplicate human milk by any process of 'humanization' of cow's milk:

They told him it couldn't be done.
With a smile he went right to it:
He tackled this thing that couldn't be done,
And found he couldn't do it!"

Little indeed is known of optimum nutrition. What is optimum? Is the comparatively higher protein content of cow's milk a good thing, a bad thing, or doesn't it matter? When does it matter? If the solute load of unmodified cow's milk is too high, why reduce the protein and salts? Why not simply add water? It's cheaper. If there are too many calories derived from protein, why not continue with the conventional methods of formula construction by addition of sugar and water or the giving of fruits and fruit juices separately from an early age?

Shein[13] urges propaganda in favor of the use of Slob*bovilac*. Giving a name to a common object alters and enhances its attributes, he claims. It becomes more attractive and desirable. Slob*bovilac* is in any event in very extensive use, either in the form of the processed liquid, the evaporated variety, or the powder. Here is an opportunity to promote its worth and to use the fortunes saved in fundamental research. Here is a milk whose constituents have not been tampered with; here is a robust and realistic 3.5 per cent of protein, ample minerals and vitamins, cream rich in saturated and unsaturated fatty acids to the tune of 3.5 per cent fat; lactose is the sugar, 4.0 per cent of it. There has been no chemical manipulation, no emasculation, no bastardization based on the sheerest fantasy. Here is a fine and natural product, uncheated of virtue: Slob*bovilac*, Best for babies. Another name for Slob*bovilac* is cow's milk.

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P.S.: Unfortunately, with the exception of Paskudnik's contribution, I seem to have mislaid the other papers mentioned above. Considering that they are published in rather inaccessible journals, I would be grateful to any reader who would be good enough to send me a copy of any of the above papers. As regards Paskudnik's effort, I shall attempt to translate and disclose it shortly.

To the Editor:

A new term has appeared in print in the last year or more—the New Pediatrics. It has not been clearly defined, but by implication should be a better kind of pediatrics than that of the recent past. What is the New Pediatrics? Is it that of the teaching and research hospitals, where patients are studied by elaborate and expensive methods? In private practice patients needing such study are few and far between. Or is it the kind of pediatrics which overemphasizes the emotional and psychological factors in every aspect of infancy and childhood, even in the simplest physiologic reactions? Too much emphasis on such matters makes nervous wrecks of some mothers by inducing abnormal introspection.

Where may we observe the practice of a New Pediatrics? We naturally look to the generation recently trained by the best schools and hospitals. Only one in active practice comes in close contact with the pediatrics in current use. The schools and hospitals are, in general, cloistered institutions; their contact with the world of private practice is mainly through the acute or obscure cases referred for diagnosis or treatment. Few of the educators have ever been in practice, and many of them were taught by full-time men.

In an active practice patients come from all over the country because of the great internal migration of today. A study of their histories gives a picture of the kind of pediatrics which is current; consultations add to this information. The patients who have been under the care of many of the pediatricians trained in recent years have received all sorts of remarkable advice, so far from sound and so varied that it must have been evolved by the individual practitioners. Obviously they have not been taught the fundamentals based on the experience of the profession.

Over the years I have asked many young physicians whether the education they received in school and hospital had fitted them for private practice. With the exception of the graduates of a few schools, they have replied that it had not; they had been compelled to work out their own methods by trial and error—the hard way. The reason for this situation is not hard to find. The intense and easily understood interest in research completely dominates the centers of pediatric teaching, and it is held up to students as the only activity worth while. In one school, out of 19 fellows and residents not one was headed for private practice, and one of the professors said, "We are training men for research, not for practice." It is natural that the student thinks that private practice is good enough only for second raters. Many students are led into a life of research when they were better fitted for the care of patients. If an individual has the capacity to see problems needing solution, he will find plenty of them

among his private patients. Many excellent papers have been published from material collected in practice.

The greater part of private practice lies in a few areas. A brief enumeration of some of the most common errors illustrates the results of inadequate preparation.

Infant feeding makes up the largest field of practice, but in some schools there is little teaching of the subject. The result is that breast feeding is rarely used; artificial feeding is almost always overfeeding. The newborn is offered 60 to 80 calories per pound, twice what he needs in the first weeks. The older baby gets over 60 calories per pound as a rule. The fad of demand feeding tends to make parents feed the baby too much and too often. Early feeding of solids is carried to an extreme; the baby often is given more food in his first months than he can take in his second year.

The hygiene of infancy and childhood is an area in which parents need much help. Many children who have been under pediatric care have errors of hygiene in almost every aspect of their lives. These things seem trivial to educators, and a bore to teach, yet ignorance of them may break a young pediatrician.

The psychological problems of the child and parent should lie within the province of the pediatrician. To refer them to the psychologist or psychiatrist often does more harm than good. Common sense will solve many of them.

The care of acute illness involves more than a shot of penicillin, the first and last thought of many physicians; the care of the sick child demands a definite schedule, treating the child more than the disease. Diarrhea is commonly treated with skimmed milk and kaolin pectin mixtures, and the results are often bad. Even some books advise a full diet at the outset with no treatment until severe symptoms develop. Severe diarrhea is not seen in private practice, if the intestinal tract gets the rest to which it is entitled in the early stages.

The common infectious diseases bring many questions to the young pediatrician which he must be ready to answer; the teaching in many schools does not prepare him to do so.

Many other examples could be quoted in other areas if space permitted. Much of the above material could easily be taught in lectures or large group conferences; to teach it to individuals involves too much repetition, so it is never taught.

The cost of medical care is completely disregarded by many physicians. Expensive drugs are ordered without good excuse. Children, who could be better cared for at home, are sent to hospitals, incurring needless expense which the young parents can ill afford. The psychological trauma of leaving home is not to be disregarded, and cross-infections and accidents in the hospital are not rare. The physician who assumes responsibility for the care of a child should be ready to make necessary house visits for acute illness. Laboratory tests and other diagnostic aids are ordered with little consideration of the costs by many physicians, and when not really needed. Recent surveys have shown that less than 1 per cent of the laboratory work done in hospitals yields positive information.

The young doctor who decides that private practice is not beneath his intellectual dignity starts out with the feeling that he has been trained to cope with any pediatric problem. He soon finds out that he does not know the answers to the simple questions of everyday practice. He cannot be blamed for feeling resentful toward a system which has failed to give him a useful education. He must teach himself how to handle his patients, and may never work out many of the things which have been learned by the experience of others. It is easy to understand why there is such a wide variation in the advice given to mothers, advice which is confusing to them, and often unfortunate for the children.

What is the future of private practice in pediatrics? The rapidly increasing population of the country will need many more practitioners. Already good openings in first class groups are going begging, or are being filled inadequately. If only the less able students go into practice, and if they continue to receive unsatisfactory training, it is likely that the care of children will deteriorate further. Should not better care of the children of the world be considered as a worthy ideal by medical educators?

What rewards are offered by private practice? They are many: a better living for the physician and his family than is likely under research grants, which have an unfortunate tendency to run out; a wider and better choice of a community in which to live; a position of honor among his fellow citizens; the satisfaction of watching children grow up in good health under his care; the friendship and gratitude of parents for bringing their children through serious ill-

ness; and, at the end, the feeling that he has been of some use in the world. These satisfactions might well be held up before students of medicine, and compared with the probable returns from a life devoted to research, for all but the exceptional few.

What is the New Pediatrics? How does it differ from what we might also capitalize as Good Pediatrics? A really good pediatrician knows the scientific aspects of the subject, and makes time to keep himself up to date by continuing study. He takes complete histories, not only of past and present illness, but also of the child's health habits, and of the psychological problems of parent and child. He makes thorough physical examinations, and repeats them again and again. After study of the child he decides on necessary laboratory work, but omits expensive routine tests which are unlikely to be essential. He keeps accurate written records of every contact with the patient, including telephone calls, and hospital, as well as office and house, visits. He gives full written directions for all treatment, never relying on oral instructions, and takes time to make sure that his advice is clear to the mother. He impresses on the parents the importance of periodic health examinations throughout childhood, as well as infancy, and includes in them a repeated analysis of health habits. He warns the parents about the dangers of adolescence. He considers the financial status of the family, orders no more expensive drugs than necessary, does not send children to the hospital for minor illness, or merely to suit his own convenience, and adjusts his fees to the family income. If he is a good pediatrician he will be able to follow his patients through childhood and adolescence, perhaps until they are married, and may hope to see their offspring, even their grandchildren!

In what respects is the New Pediatrics different or better?

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To the Editor:

In the March, 1960, issue of THE JOURNAL OF PEDIATRICS, page 383, there is a paper entitled, "Pseudohypoparathyroidism and Pregnancy."

Because of the statement in it to the effect that "no other report of pregnancy in a pseudohypoparathyroid patient has appeared," you may perhaps wish to know about another such case which has been documented in the literature.

The case is described in an article entitled, "Pathohistological Aural Changes in the Progeny of a Mother With Pseudohypoparathyroidism," which appears in the *Annals of Otology, Rhinology and Laryngology*, December, 1958, vol. 67, page 964. The infant described in this instance died 1½ hours after birth.

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EDITOR'S COLUMN

In defense of pediatrics

NOWADAYS whenever a group of pediatricians chance to gather in the proverbial cloakroom huddle, or even meet as a committee for this or that purpose, sooner or later the conversation invariably gets around to a discussion of what's wrong with pediatrics. At such a meeting recently I was dismayed to hear several heads of pediatric departments along the eastern seaboard emphatically declare that the current adverse criticisms about pediatrics unquestionably were steering medical students and interns away from pediatric careers. This, I believe, is most unfortunate. It would appear to be high time that something be said in defense of pediatrics.

At the outset I should like to express my conviction that the term "pediatrics at the crossroads" implies a critical status for the future of pediatrics which is not merited. As I look back over the nearly 40 years that I have been in the practice of pediatrics, I am tremendously impressed by the contribution it has made to the total progress of medicine. It has brought to American children the highest quality of medical care in existence anywhere in the world. In 1948 there were approximately 2,500 members of the Academy of Pediatrics. Today there are more than 6,000. Up to April 30, 1948, the American Board of Pediatrics had issued 2,792 certificates. To date 7,272 certificates have been issued by the Board. In 1948 there were 791 residency appointments available in approved pediatric services. In 1958 there were 1,779, or 2½ times as many. In 1948 the number of candidates examined by the American Board of Pediatrics was 210. Approximately 500 candidates are now examined each year. All of these statistics clearly show that up to now there has been no lack of interest in pediatrics as a specialty. At the same time important advances have been made in all university pediatric departments since the Academy's survey in 1947. Research projects both in quality and quantity have increased enormously, and pediatric medical literature has achieved new heights. There is no reason to believe that these brilliant accomplishments of the past will not be continued in the future. Why, in view of all the progress pediatrics has made and is making, should there be this sudden concern for its future? To be sure, well–thought-out changes will and should be made as they have been made in the past, but I cannot go along with the view that pediatrics as of the present is in such dire straits that heroic modifications must be instituted to rescue it from failure and oblivion.

I am aware, however, that for the last several years rumblings and criticisms about pediatrics as a specialty have been heard with increasing frequency. Among those of a more disturbing nature the following might be singled out for comment: (1) the practice of pediatrics does not provide a satisfying professional career; (2) interest in pediatrics

as a specialty is decreasing; (3) the quality of physicians attracted to pediatrics is not as high as in former years; (4) pediatrics as a specialty should be abandoned; (5) the required residency training period should be lengthened to 3 years; and (6) the role of the pediatrician needs clarification in order to know what his education should be.

First, let us look at the criticism which should perhaps be of most concern to all of us, practitioners and professors alike: that the practice of pediatrics no longer affords a satisfying professional career to an increasing number of pediatricians. Adherents to this point of view refer to a survey reported in *Medical Economics* a few years back in which it was stated that a third of practicing pediatricians polled expressed dissatisfaction with the practice of pediatrics and indicated that they would not go into it again if they had it to do over. The reasons cited include long hours, hard work, low pay, and the monotony of practice as compared to the glamour of residency training. As one individual put it, he was trained to be a race horse, but in practice found he was running a milk route.

How seriously this rather severe indictment of the present-day practice of pediatrics should be taken is questionable. If it merely represents the views of a relatively small number of individuals who for varying reasons found themselves unhappy, then it can be dismissed. On the other hand, if it is true as stated in the survey by *Medical Economics* that a third of practicing pediatricians are dissatisfied, it is a problem that must be faced. I have no idea of the geographic area covered by *Medical Economics* in their sampling, but I suspect more dissatisfaction might be found among pediatricians in large cities along the eastern seacoast where competition is keenest than elsewhere in the country. My own observation based upon a fairly wide acquaintance among the pediatricians of the Middle West and upon conversations with many of them would lead me to believe that the great majority of practicing pediatricians scattered over the country are thoroughly satisfied with their jobs, their incomes, and with the amount of work required. One wonders if a survey made of other specialty groups, such for instance as internal medicine, would not turn up its quota of individuals who would feel the pastures were greener on the other side of the fence.

The complaint of dissatisfaction with pediatric practice because of an unprepared-for letdown due to the infrequency of exciting cases as compared to their commonplace occurrence in residency training is a matter of real concern. One may properly ask the question whether residency training in pediatrics as it is carried out in many of the large medical centers is suitably oriented to the needs of pediatric practice as it is presently constituted. Is it overweighted in favor of the unusual and is it inadequate in the commonplace? Should there be another year of training devoted to the emotional problems of the child and the adolescent and to a better understanding of the role the pediatrician should play as a counselor in family relationships? Would not such additional emphasis, whether it be incorporated in the present 2-year period or added in a third year, permit the pediatrician to view in a more interesting light the endless questions of mothers in office practice and give him better insight into the importance and dignity of being the purveyor of sound parental advice in building solidarity of the family structure throughout the period of growth and development? No one would argue, I think, that this type of training should be at the expense of sound training in basic concepts of a wide variety of disease processes, for the pediatrician must be prepared to recognize and manage the occasional unusual or complicated emergency problem which may occur in his practice or be referred to him as a consultant. But perhaps more thought could be given on the part of educators to a better orientation of training programs to the needs of practice, especially for those pediatricians-in-training who indicate early their intention to be practitioners. On the other hand, I find it difficult to understand why the pediatrician who has decided upon practice as a career does not ascertain for himself beforehand

what private practice is like. It seems absurd that as many as a third of pediatricians who go into practice should be so uninformed as to be disillusioned and dissatisfied by what they find. A week or two spent in the office of a pediatrician in private practice sometime during the 2-year residency period might well be a rewarding experience for the prospective practitioner.

Presumably, it was knowledge of criticisms about pediatric practice that prompted Dr. May to publish his much discussed editorial in the February, 1959, issue of *Pediatrics* entitled, "Can the New Pediatrics be Practiced?" By the "new pediatrics" he would appear to mean the high quality of comprehensive medical care the well-trained pediatrician is equipped to dispense, but which the public is not educated to pay for. The result is frustration and disillusionment when the pediatrician finds himself unable to do what he believes he should do because of economics. He sacrifices quality for quantity in order to make possible the income he feels entitled to, Dr. May states, "There is no use turning out better and better trained pediatricians unless they can put their knowledge into practice," and he poses the question, "Is the pressing problem not to bring the public to recognize and be willing to pay for the best of professional guidance and treatment before some other enterprising group persuades the public that a little knowledge of child care can be applied by any general practitioner to meet their needs at the attractive price possible with mass production and quick turnover?"

Dr. May's argument merits consideration. It may well be that pediatricians have been derelict in their failure to set a market value upon their services comparable to that, let us say, of internists. But if pediatricians have been derelict in this respect, a ready and plausible explanation would appear to be that the majority of their clients are young adults who have not as yet acquired the means to afford fees the pediatrician would have to charge for comprehensive care for a limited number of patients. Furthermore, pediatric office practice differs materially from that of the internist. The latter, in his well-patient care, sees his adult patients ideally once a year. In addition to the usual history and physical examination, an electrocardiogram, chest x-ray, blood count, and urinalysis are accepted, even demanded, as constituting an adequate checkup. For this the adult expects and willingly pays a good fee. No such extensive examination can or should be carried out by the pediatrician for his routine well-child checkups. Consequently he must see 3 or 4 patients to earn the same fee the internist gets in seeing one. The pediatrician is in trouble when in the course of his afternoon appointments scheduled at 15- to 20-minute intervals he encounters a mother with a problem in the mental health field which by its nature is bound to be time consuming. Here, the "new pediatrics" may have its application. Under the "old" system he might attempt to solve the problem by hurried advice offered within the limits of the 15- or 20-minute appointment. Neither he nor the mother would be satisfied, and the child in all probability would not be benefited. In the "new pediatrics" he would recognize the time requirement and would set up one or more appointments of longer duration for full exploration of all factors involved. His fee should be commensurate with the time spent, but more important would be the satisfaction derived from a job well done. It is difficult to see how the "new pediatrics" could have application outside the mental health field. In the study and management of ill patients the pediatrician's approach and his fees differ little from the internist's.

The criticism that interest in the specialty of pediatrics is decreasing is not borne out by available data. Earlier I mentioned the remarkable growth of the American Academy of Pediatrics and of the American Board of Pediatrics. Until recently the Board of Pediatrics was the third largest among the 18 Boards. At present I believe it is fourth. Previous to the war the number of candidates examined each year seldom exceeded 100. In 1948 the number was 210; 299 in 1949; 390 in 1950; 391 in 1951; 512 in 1952; 509 in

1953; 524 in 1954; 476 in 1955; 419 in 1956; 497 in 1957; 514 in 1958; and 537 in 1959. The percentage of available residencies filled in pediatrics in 1957 to 1958 was 86 per cent, which was well above the national average for all specialties. What per cent of these was filled by graduates of foreign medical schools, I do not know. Thus there would appear to be no alarming decrease in interest in pediatrics among medical students and interns as far as numbers go, at least up to the present time. The question about quality of residents going into pediatrics is more difficult to answer, and must rest upon opinion rather than fact. My personal view from observing a fairly large number of candidates at the time of their examination would be that the quality is essentially unchanged. I think the Board's examination has been stiffened somewhat over the last few years and that the performance of the candidates has kept pace with the increased requirements. The rate of failure at any given examination for the last several years has closely approximated 20 per cent. As might be expected, one observes in any examination session a few superior candidates, a few very bad ones, and many in-between ones.

The fourth criticism listed was that pediatrics as a specialty should be abandoned. The suggestion was contained in a letter to the Editor published in the May issue of *Pediatrics* in response to Dr. May's earlier editorial. This is not the first time this suggestion has been made. It was made some 20 years ago. I have forgotten by whom, but his argument was that the problems of infant feeding had now been solved, and there was no longer need for pediatricians. How wrong he was surely has been demonstrated beyond question in the last 20 years. The more recent advocate of abolishing pediatrics as a specialty would direct education in pediatrics to the general practitioner who would then care for some 90 per cent of children's medical needs. The remaining 10 per cent representing the more difficult problems would be cared for by the internist. He would incorporate a year of training in pediatrics into the training of the internist to qualify him for this additional role. I do not believe this point needs to be pursued further. The arguments against the contention that pediatrics has outgrown its period of usefulness are even more substantial now than they were 20 years ago.

Now, let me turn to a more controversial problem—that of increasing residency training requirements from 2 to 3 years. This issue is well past the rumor stage. It has many advocates, both practitioners and academicians, and is being pushed vigorously by a few. Those who argue for 3 years of training cite the great increase in the total body of knowledge which has accumulated in recent years and the difficulty of cramming into 2 years what is considered necessary to constitute a well-rounded training experience. In addition to the usual inpatient and outpatient experience, reference is made to the desirability of instruction in laboratory techniques, electrocardiography, electroencephalography, radiology, and in the subspecialties of hematology, endocrinology, neurology, allergy, cardiology, psychiatry, pathology, and research. To these I presume will now soon be added the subspecialties of genetics and enzymology. Why, they ask, should it take more years of training to be a physician for adults than it does to be a physician for children? Pediatricians who have had 2 years of training, they maintain, are at a disadvantage in their hospital relations with the internists who have had 3 years of training. This disadvantage obtains also in practice when the pediatrician may be forced to relinquish his diabetic, hematologic, neurological, and similar disorders to the internist with special training in these categories, thus leaving the pediatrician with little else but minor ailments and well-child care. Furthermore, they maintain, the practicing pediatrician with only 2 years of training who serves part time on the staff of the teaching hospital is not qualified either to diagnose and manage, or to use for teaching purposes, patients with the more unusual illnesses. Finally those who argue for an increase in the training period believe the dig-

nity of pediatrics as a specialty would be elevated, and that it would then be on a par with all the other specialties in medicine. As a result, they feel both the number and quality of physicians who would be attracted to a pediatric career would be increased.

Now let us take a look at the other side of the coin, for there is another side. There are many, including academicians, who do not agree that the 2-year training period should be increased to 3 years, at least not at present. For instance, at the April 25, 1959, District I conference on medical education, attended by some 13 representatives of New England medical schools, there was only "one half-dissenting vote among an avalanche of opinions that it would be best to leave the 2-year residency requirement as it is."

The statement has been made that it is futile to discuss training requirements until pediatricians make up their minds what the role of the pediatrician should be, hence, what his education should be. It seems perfectly clear that pediatricians are and should be trained for general practice among children, for consultants in medical centers, for academic careers, for public health, and for research. Among these the largest number by far are the pediatricians in practice. It is my impression that among a group of 10 residents in the average training center, approximately 8 will elect and be better suited for practice than for an academic career. Obviously the desires and qualifications of the individual dictate the course he follows. Under the present 2-year system in which a large number of pediatricians have been turned out to serve as general physicians for children, no one can deny that a tremendous contribution has been made to the health and welfare of American children. Initially, only the larger urban areas attracted pediatricians, but as time has gone on, communities with as few as 10,000 inhabitants or fewer have demonstrated that they can support a satisfactory pediatric practice. There is abundant evidence that the need for this type of pediatric care is far from being met. Hardly a week goes by that I do not receive one or more requests for help in securing a pediatrician for a community or for a clinical group. When the time comes that general practitioners have increased their training requirements to include a minimum of 6 months in pediatrics so that provision will be made for maintaining a good standard of medical care for children, training requirements for pediatricians may well be increased to 3 or even 4 years with the objective then of creating a body of consultants. But until that time comes, it is my belief that the present 2-year requirement, modified perhaps in educational content to meet better the needs of practice, will best serve the health requirement of American children.

I should hasten to add, however, that I am equally convinced that efforts should be made to encourage by all means possible a greater number of pediatric residents to obtain training beyond the 2-year level. Such individuals are sorely needed in academic fields and in research in the university setting. There is real need for them also in private practice, especially in the larger urban areas, where their superior training would qualify them to serve as consultants. There is a tendency at present for scholarships, loans, and grants to be restricted to the 2-year training period either to encourage interns and medical students to enter pediatrics or to enable those in financial distress to complete the second year of training. While this is laudable indeed, it is my feeling, nevertheless, that equal financial support should be made available to those who desire training beyond the second year. If training grants for married pediatricians with families could be upped to a living wage, the problem of attracting qualified individuals along the academic pathway would be considerably eased.

Also, in this question of 2 versus 3 years of residency training for pediatric practice, there needs to be considered what the content of the third year of training would be and what would be its effect in terms of decreasing or increasing dissatisfaction with practice and in terms of decreasing or increasing the numbers attracted to pediatrics.

Presumably the extra year of training would be in the subspecialties, as for example 3 months each in hematology, cardiology, neurology, and allergy. Or a full year might be devoted to one subspecialty such as hematology or cardiology. No one, I am sure, would question the personal satisfaction a resident who elects a third year of training, even though he goes into practice in a small community, would derive from more training in one or several of these subspecialty disciplines, but there is the distinct possibility that the infrequency he might find to apply his extra knowledge in practice might well prove to be disheartening. On the other hand, if he located in a sizable urban community with the facilities of a medical center at his disposal, he would be in a position to utilize his extra training in the capacity of a consultant to both general practitioners and practicing pediatricians in the smaller surrounding communities, and his value as a member of the part-time teaching staff would unquestionably be enhanced. Perhaps then, there is need for 2 types of practicing pediatricians. One is for general physicians for children, many of whom will locate in small communities away from the medical center and whose training will permit them to render a high quality of comprehensive medical care to their pediatric patients. The other is for pediatric consultants whose specialized training in one or more pediatric subspecialties necessitates an urban setting in close proximity to a medical center. The educational requirements of the 2 groups are not necessarily identical. Numerically the group with 2 years of training in practice is many times larger than the consultants, academicians, researchers, and those in public health combined. It seems logical that the formal residency training requirement should be directed to the needs of the large body of pediatricians who wish to go into private practice. Those desirous of extra training to qualify for a consultant's role or who elect to remain in the academic setting would be free to make whatever arrangements they wished above and beyond the required basic 2-year training period. Three years of training should not be made mandatory for all pediatricians in order to meet academic needs.

The most crucial question demanding an answer in the argument over 2 versus 3 required years of residency training would appear to be this: can an adequate training be given in 2 years to meet the needs of the pediatrician in practice? From my own limited experience in participating in a residency training program in a private hospital sensitive to the needs of private practice, I would say the answer is yes.

Finally some thought should be given to the difficulties which would be encountered by training centers if a third required year for Board certification were added. There are approximately 254 approved training programs in the United States. Of these some 82 are university-connected programs. Assuming that all the training programs connected with medical schools, and this is probably a generous assumption, would be capable of offering a profitable third year of training, there would still remain a tremendously difficult problem of putting a compulsory third year of training into effect. Probably not many of the 172 nonuniversity-connected programs would have the facilities for setting up a worth-while third year. The result would inevitably be that many of these would have to abandon residency training or would install makeshift third years which would be largely wasted time for the resident. Certainly the 82 university-connected centers could not assume the task of training all the residents in pediatrics nor could they agree to provide the third year for all nonuniversity connected programs incapable of providing a third year on their own.

In conclusion I should like to call attention to an editorial written by Dr. Arthur Parmelee in the April, 1957, issue of the *Medical Bulletin* of the Los Angeles Children's Hospital entitled "Pediatric Rewards." It was republished in the December, 1957, issue of THE JOURNAL. Clearly, no one but a mature individual who had experience and who has grasped the significance of the sat-

isfactions to be derived from long and intimate contact with children could have written such an editorial. It is to be hoped that many young pediatricians who may be in the initial throes of disillusionment with pediatric practice will read what Dr. Parmelee has written and will take heart from his words of wisdom. I should like to add that I wholeheartedly share his feelings about the rewards afforded by pediatric practice, rewards not to be reckoned in terms of monetary value, but rewards many times richer in terms of intimate and lasting friendships made over many years with colleagues, with parents, their children, and now with the children of former patients.

Perhaps I can best summarize my thoughts about pediatrics by quoting from a letter I received recently from one of my residents who began practice in a small city in Idaho on July 1, 1959. He joined another former resident who had been in practice some 6 or 7 years.

"Even though there have been many articles and letters written recently about the dissatisfaction many pediatricians have with their field, I certainly can't substantiate this feeling as based on our practice so far. Of course my partner gets most of the referred patients all of whom I see with him, and when he is out of town, I see them first hand. Then, too, we see patients from many miles around for routine care. One six year-old boy from 105 miles away came in for a pre-school examination. Several days ago I cared for a newborn from Jackson, Wyoming, which is also about 100 miles away.

"We added up our exchange transfusions the other day and found we had done 22 since I came on July 15, 8 or 9 of which I have done. Eight of these were in a one week period several weeks ago. My first one in August was a 24 hour old infant with a bilirubin of 34 mg. % when I saw him. Luckily he pulled through with no evidence so far of kernicterus after three exchanges.

"This past week we've had the following patients in the hospital: an eight months-old boy with a primary hepatoma resected after some 5 hours in surgery; a 14 year old girl admitted in diabetic acidosis and semi-comatose whom I cared for and finally got squared away; a two year old girl admitted three days ago with a bacterial meningitis who is now clearing slowly; a newborn with cyanotic congenital heart disease who has been transferred to Salt Lake City for angiocardiography; an 11 year old girl admitted overnight for observation to rule out appendicitis; a 1½ year old baby with gastroenteritis and in addition 5 to 10 newborn in the two hospitals. Not all the weeks have been quite so filled with such a variety of cases but other patients we have had include a four year old child with lipoid nephrosis; a seven year-old with a patent ductus sent to Salt Lake City for surgery; a 10 day old premature male with a duodenal atresia who had been vomiting, of course, since birth but who finally managed to survive; a boy with newly diagnosed diabetes to be regulated; a week old infant with convulsions found to have a massive sub-dural, but who died during surgery; and now we have a possible Vitamin D resistant rickets whom we are about to study.

"Some of the authors writing about the 'New Pediatrics' have certainly mentioned one of the problems—that of the value to be placed on referred patients and the amount of time spent in caring for them. As my partner said several days ago, 'If our practice was much more interesting, we couldn't afford it.' But I must say I am enjoying practice thus far with some reservations concerning night calls—the nights get quite cold here and without a garage its rather chilly at 2:00 A.M."

I believe the great majority of practicing pediatricians could write similar letters indicating that pediatrics can and does afford a satisfying professional career. Because of the urgent need for more pediatricians, especially in the smaller communities throughout the country, the advantages of pediatric practice should receive emphasis. Medical students and interns ought not to be turned away from pediatric careers by criticisms emanating from a relatively few who in all probability were not constitutionally suited to

practice in the first place. The basic residency educational program should be designed to meet the needs of the pediatricians in practice. Two years of residency training has demonstrated its adequacy to meet the needs of this group. Training beyond the 2-year level is to be encouraged by all means possible, but this should be the responsibility of the training center and of the individuals who want more training.

LEE FORREST HILL, M.D.

The case for the 2-year residency training program in pediatrics

THIS editorial results from a proposal that the required period of residency training in pediatrics be increased from 2 to 3 years. It was written originally in September, 1959, as a letter to Doctor Lee Forrest Hill, then President of the American Board of Pediatrics, to present the personal views of the writer on this proposal. It is submitted for publication at his request and with the agreement of the American Board of Pediatrics. While it might be looked upon as a justification for the present 2-year residency training requirement of the Board, it is not an official statement of the Board, nor should it be inferred that the views here expressed are necessarily held by all present members of the Board.

While the writer's interest in this problem stems primarily from his position as Executive-Secretary of the American Board of Pediatrics, his views are modified by his experience as a practitioner of pediatrics and as dean of the medical school, as well as by other activities related to residency training. He hopes that this combination of interests may add perspective to his views on the subject.

With a few minor modifications, the letter sent to Doctor Hill follows:

THE PRESENT SITUATION

It is my belief that the present 2-year residency training program has been extraordinarily successful in producing a large number of pediatricians well qualified for the medical care of this country's children. Practicing pediatricians have been scattered far and wide throughout the land and a constantly increasing number of children are being cared for by them. At the time of the academy study in 1947, there were about 3,500 physicians who listed themselves as pediatricians, of whom about 1,800 (51.4 per cent) were certified. It was estimated that about 15 per cent of child medical care was performed by this group. There are no exactly comparable figures available today, but the 1958 American Medical Directory records 7,473 full-time pediatricians and 5,469 Board-certified pediatricians in the United States, a threefold increase in the latter and 73 per cent of the total. The Directory of Medical Specialists for 1958 shows about 5,900 Board-certified pediatricians or 79 per cent of the above total. An additional 1,821 physicians are shown as part-time pediatricians by the American Medical Directory. Meanwhile, between 1949 and 1957, the number of general practictioners and part-time specialists decreased by approximately 13,600. Therefore, beyond a reasonable doubt, both the number and percentage of children cared for by pediatricians has increased significantly since 1947.

Thus there has been created in the United States a situation quite different from that existing in most countries where there are but a relatively small number of physicians engaged in the practice of general pediatrics throughout the community. Their pediatricians are primarily consultants or staff members of the larger hospital services for children.

I submit that under the plan of certification set up by the Board, pediatrics has brought the medical care of children in the United States to levels that would not have been attained under a system whose primary concern was with the production of consultants.

Effect of 3-year residency requirement. No one knows the ultimate effect of a 3-year resi-

dency training requirement on the number of physicians who would enter pediatrics. There is no doubt, however, that for a period of years immediately following its adoption, the number starting practice would be decreased materially and I personally fear that the number of physicians entering residency training in pediatrics might be reduced significantly.

Figures compiled by the Surgeon General's Consultant Group on Medical Education, of which I had the honor to be a member, show that because of estimated increases in population, by 1975 we will need to graduate about 3,600 more physicians each year than we do now simply to maintain the physician-population ratio at its present level. It will be very difficult to meet this demand, and any action on our part that would delay or reduce the number of physicians entering the practice of pediatrics in the years just ahead would, to my mind, be a serious disservice to the children of the country.

In recent years there has been much discussion in medical education circles concerning the desirability of shortening the elapsed time between admission to medical school and the opening of specialty practice, and some medical schools have already embarked on efforts to accomplish this end. Many times the American Board of Pediatrics has been complimented by thoughtful men in medical education and in posts of national administrative importance for maintaining its 2-year residency training requirement.

While elective programs for additional residency training for selected individuals should certainly be encouraged, on the basis of the need for practicing pediatricians in the years just ahead, I feel that it would be a serious mistake to increase the requirements for all pediatricians at this time.

Comparison with internal medicine. The specialty most nearly akin to pediatrics is internal medicine. The fundamental difference between the training programs of the two specialties rests on the fact that while pediatrics requires a standard 2 years of residency training and 2 years of practice or further study, internal medicine offers a sliding scale of years in residency and practice. Thus while the basic requirement (Plan A) is 3 years of residency and 2 years of practice, under Plan B a candidate may qualify after two, one, or even no years in residency training by substituting "continuous experience in the broad field of internal medicine at the rate of 3 years of such experience for each missing year of formal residency or fellowship training."[1]

Personally, I far prefer the pediatric plan to that of internal medicine. It places more emphasis on a *standard* period of training and less dependence on examination. It may also be the explanation of a lower rate of failure in pediatrics.

Comparison with foreign training programs. Any comparison with foreign requirements should be approached with great caution because of the risk of misinterpretation of the exact meaning of terms. Thus, at the recent World Conference on Medical Education I learned that in some countries the stated period of residency training can be served on a part time basis, the candidate carrying on practice at the same time. Further, most of these countries are training pediatricians for a consultant type of practice rather than general child care. Thus in France 72 physicians applied for training and 35 were accepted for 1959.

Training centers and 3-year requirement. A residency training program should be restricted in duration to its educational potential, for mere repetition of technical procedures is neither necessary nor useful to the trainee.

Dr. Walter Seelye tells me that of the pediatric residency training programs he has surveyed personally for the Residency Review Committee for Pediatrics in the past 3 years, it is his considered opinion that only 9 out of 40 (22.5 per cent) would have been capable at that time of adding a third year of satisfactory training. In a very rough check of the 288 approved programs in pediatrics listed in 1958, I estimate that about 80 (28 per cent) might now be able to qualify in this regard. Even among these there are some services that now want to move their trainees entirely into subspecialty fields after 1 year of straight internship and 1 year of general residency. They apparently find it difficult to fill this third year out of medical school with general residency work.

Hence, even if other considerations seemed to indicate a change, I feel that it would be a mistake to increase the training requirement to 3 years until we have good evidence that a far higher percentage of services are ready to implement this through programs of high quality. To do so now would be to re-create a situation worse than that which existed a few years ago

when we started to do away with hospital programs which had been approved for only 1 year.

I do not know the source of the impetus for a third year of residency, but I suspect that it comes chiefly from some of the larger training centers that for perfectly understandable and laudable reasons want pediatricians trained in a subspecialty. With these objectives I have great sympathy, but in deciding what is best for ourselves, let us not forget what is best for the community. It is the obligation of the Board to establish regulations that will guarantee that its diplomates are well qualified for the practice of pediatrics but that at the same time will stimulate the flow of practitioners to the community; it is not the Board's obligation to set requirements suitable for subspecialty trained faculty and hospital staff members; it is not its obligation to provide teachers and investigators. That is the obligation of the schools and their faculties. As a Board we should, and I am sure will, do everything in our power to help them obtain and retain suitable trainees, but it would be wrong for us to force a third year of training on all pediatricians in order to meet the desires and needs of a small group of academically directed candidates if that third year of training is not clearly needed for the practice of pediatrics. I, for one, do not think that it is needed, for I believe that our practitioners are doing a highly commendable job.

Accordingly, I am forced to the strong conviction that a required increase in the duration of residency training in pediatrics in the near future is uncalled for and would be unwise. I would be moved from this conviction only by a clear mandate from practicing pediatricians that an extra year of residency training is necessary to prepare them properly to meet the medical demands of practice.

JOHN MC K. MITCHELL, M.D.

REFERENCE

1. American Board of Internal Medicine: Memorandum to Candidates for Admission to Examination, Nov. 1, 1959.

Further thoughts on preparation for pediatric practice

INASMUCH as I have on occasion expressed opinions on training for pediatrics which might seem to be somewhat contrary to those of Drs. Hill and Mitchell, it would seem appropriate for me to state my position in these columns. In brief, if there are differences in our points of view they are of a minor degree and largely, if not entirely, are limited to the third year of residency training. Each of these men has had extensive and unique experiences in pediatric practice and in educational programs, and no one is in a better position than they to evaluate the over-all situation in pediatric practice throughout this country through their many experiences on the American Board of Pediatrics. Their views as expressed are of great importance in the present considerations concerning the pattern of pediatric practice and preparation for it.

Preparation for pediatric practice actually begins in childhood as it does for any of man's roles. But within our immediate sphere of responsibility, it begins with the admissions committee of the medical school, whose responsibility for the selection of candidates with adequate potential for the practice of medicine must be emphasized repeatedly. Medical school experiences are crucial. Here I am confident that the three of us have no essential differences of opinion. The student must have a solid foundation; there must be no compromise with a goal of knowing what is known and what is not known of the functional activities of the body. The physician must be able to approach disease on physiologic-pathologic and anatomic-pathologic bases, and he must depend as little as possible on empiric formulas. The student who lacks curiosity and the capacity for critical appraisal cannot be expected to become an adequate physician. Objectively one must recognize that there are great differences among medical schools and within the various depart-

ments of the individual schools in the degree to which these characteristics are stimulated and fostered.

The internship must be considered as being of equal importance with the residency. This is not the place for a discussion of the relative merits of the rotating internship versus those of the straight one, but it can be emphasized that all too many internships seem to be designed for service to the hospital and its medical staff rather than for the training of the young physician.

The residency years in pediatrics should be designed primarily to prepare the young doctor for practice, not for an academic career. He must continue to strive for more thorough knowledge of known physiology and for the capacity to apply such knowledge in the evaluation of a given patient. I hold no brief for those who suggest we should teach "short-cuts" and so-called practical methods or rules-of-thumb for various medical situations. These come out in ample number during the residency years, and the acquisition of them in practice comes easily and readily. I am confident that the effective individual will acquire and develop the tools of practice in his own natural pattern from his experiences during his residency years.

Lest it be deduced that my ideas of training are based on a knowledge of disease per se and not of health and disturbances of it in the individual, permit me to add that I believe one grows and develops by testing and retesting his knowledge through application of it. In pediatrics the focal point is the child in his several environmental spheres—initially his family, with the neighborhood and the school being added in succession. Pediatric training today must provide a significant proportion of this total time for experiences in the outpatient department with responsibilities for child and family guidance. Home care can be added to advantage, but only if there are ample facilities for consultation and for guidance of the resident.

There is not much probability that Drs. Hill and Mitchell and I have any very basic disagreements on any of the above. If this is so, in what respects may we differ otherwise?

For some years I have felt that a third year of training pays sufficient dividends to justify investment in it. This I have felt is especially so for the really good resident, provided he is in an environment which provides him ample stimuli. This conclusion applies entirely to the man who intends to go into practice and as much to the one going into a small city of 10,000 inhabitants as to the one who locates in a metropolitan area where there are one or more medical schools and/or pediatric centers. The man who is destined for an academic career can today usually find facilities and means for continued general and/or specialized training. He is not the issue here.

Some pediatricians have expressed a dissatisfaction with the role which they develop in private practice. Among the expressed dissatisfactions are those related to the make-up of their practice—too much of the commonplace and too little of the unusual. It has been my experience that such complaints are more apt to come from the less competent and the less well-trained men than from the more knowledgeable and more effective ones. I know of a number of young pediatricians in cities of relatively small size close by and distant from a medical school or pediatric center who not only have active and ample general pediatric practices but who also serve effectively as consultants to other physicians in their area. Such pediatricians soon develop the need for one or more assistants or partners, even in the smaller cities. It might be inferred that I have a naive conception that a third year of residency will provide per se the young pediatrician with sufficient knowledge and skill that he can "do all things." I trust that many will not so conclude. Certainly he will have to refer some of his diagnostic and therapeutic problems, but he will be able to manage some cases which he would otherwise refer. I simply cannot believe that the man who "knows more" and who is reasonably adjusted to reality will

not be the one who gets the most satisfaction out of his practice. Most men are unhappy and uncomfortable when they find themselves in situations where they are expected to know but do not.

I do believe a third year of training in an adequate setting is distinctly worth while for the man of excellent potential for the practice of pediatrics. I also believe it can help the less competent man, especially if he *chooses* to secure additional training and is not *compelled* to take it. There was a time when I thought that the American Board of Pediatrics should make 3 years of residency training a prerequisite for examination for certification. At the moment I am less certain that the third year should be compulsory. In the first place, I agree that there are probably not sufficient adequate training facilities to provide places for all of those now going into pediatrics if a third year were required. Further I would hasten to add that I too believe we would be doing a disservice to risk elimination at this time of a relatively large number of young physicians who might not choose to go into pediatrics if the period of training were extended to 3 years. I have no intent to sell these persons short; many of our best physicians are in this category. There are, however, increasing numbers of resident physicians in pediatric training who intend to go into practice and who are choosing to take a third year of training in general pediatrics, in several subspecialties, or in a single subspecialty. I am sufficiently optimistic to believe that a significant number of such trainees will find their way to the smaller cities and that they will not only be effective as general practitioners for children but also as consultants to their colleagues. I know a number of such who would not exchange their roles in their adopted community for the "benefits" of the metropolitan area.

Perchance we will be on firmer ground with more potential for growth if we keep Board-required residency years to a minimum of two and depend on self-motivation and determination for the added impetus to further improve the practice of pediatrics.

I cannot refrain from expressing here my fervent hope that the executive body of the American Academy of Pediatrics will give further evidence of their belief in the adequacy of training for the practice of pediatrics and the right of the individual to plan his own program by removing all limitations in respect to length of residency training as they apply to financial grants and/or loans which they control.

And, lest we forget, in the current stock-taking now going on, pediatrics can and will continue to stand on its own feet. Innumerable families have found help and guidance and look with confidence to their pediatrician not only for the care of physical ills and for protection against infection but even more as a family counselor. Perhaps this is the New Pediatrics, but I would wonder if it is relatively any newer than that practiced in the twenties or thirties. Then men of ability and good intent practiced with "the tools at hand" just as they do with those available today. Two-year residencies have provided the children of this country with much better medical care than they could possibly have had otherwise. Many, perhaps most, of our leading pediatricians of today are products of such a training program. Perhaps 3 years of residency training for all pediatricians would now elevate the quality of this care to a still higher level, but there is a "perhaps" that it would not, especially if it were required. The net result would depend on a number of factors, but particularly on the man being trained, on the training program, and on the people directing it. Much as I believe that a third year of training for the better than average resident is apt to be a profitable investment, I would speak against a formalized change in the present residency requirements for Board examination. Rather I would encourage those young men and women who want something more in the way of training to get it, not necessarily in a standardized residency program but when desired by individual planning and arrangement.

W. E. N.

LAWSON WILKINS

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The Journal of Pediatrics *joins his students and colleagues on the event of his 65th year in the recognition of his contributions to pediatric medicine.*